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How to overcome endocrine resistance in early and metastatic breast cancer

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Abstract

According to St. Gallen Consensus, endocrine responsive breast cancer is defined by positive steroidal receptors (ER= estrogen receptor and PR= Progesterone Receptor). ER/PR and HER2 are the most important biomarkers in decision-making about adjuvant and palliative treatment options. Available data suggest, that the higher the expression of ER and PR, the better the outcome for patients with early and advanced breast cancers.

In early breast cancer setting, there is a high risk of recurrence for patients with luminal types, even after 5 years of treatment with aromatase inhibitors. Therefore several strategies to improve outcome in these patients are applied today, e.g.: 1) extended endocrine therapy, 2) CDK4/6 inhibitors, 3) mT or inhibitors or 4) bone modifying agents like bisphosphonates.

In this review, we focus on endocrine therapy resistance in early and late stage breast cancer, including resistance's prevention, endocrine treatment and responsiveness in early and advanced breast cancer. Major Phase II/III studies for CDK4/6 and PI3CA inhibitors in the metastatic setting are discussed. Finally, strategies to prevent patients with early breast cancer from recurrence are presented.

Introduction

Breast cancer is the most common cancer in women worldwide and remains an important global health issue [1]. Over the last decade, breast cancer incidence has been increasing steadily [2]. There are several reasons for this: changes of lifestyle, use of endocrine stimulating agents, earlier diagnosis (breast cancer screening) etc.

However, in parallel to raising number of patients, breast cancer survival has been improved. Breast cancer is diagnosed in 1 of every 8 US women during her lifetime. The American Cancer Society estimated that 270,000 new cases of invasive breast cancer will be diagnosed in the United States in 2018, with 41,400 deaths [3]. Therefore, breast cancer remains an important health issue.

Endocrine therapy in early breast cancer

According to current guidelines (ASCO, NCCN, St Gallen, ESMO), breast cancer can be classified in five subtypes: luminal a (steroidal receptor positive, low Ki-67), luminal b (steroidal receptor positive, higher ki-67), triple-negative/basal like (no steroidal hormone receptor and no her2 positivity), her2-enriched

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(her2 positive**) [**4]. Each subtype has distinct characteristics and treatment differs considerably. Triple-negative and HER2 positive have the worst prognosis of all breast cancer, but especially in Her2 positive breast cancer much progress with targeted therapy have been made in the last years [5]. Luminal breast cancer is characterized by expressing Estrogen and/or Progesterone Receptor (ER, PR) and no HER2 protein. About two third breast cancer cases are ER and/or PR positive. Endocrine responsive disease is defined by expression above 1% of either ER and/or PR [4]. ER/PR and HER2 are the most important biomarkers in decision-making about adjuvant and palliative treatment options [6,7]. St. Gallen consensus defined three response groups: non-responder, intermediate and high responders. The level of steroidal receptors plays a crucial role for this definition [8]. The higher the level, the better is the response [9-13]. Endocrine therapy experienced a rapid development and is now state of the art in premenopausal and postmenopausal women with the diagnosis of ER/PR positive breast cancer [14-16].

Nowadays, there are two ways of targeting endocrine axis in breast cancer [17]. One of the first agent, which has been discovered more than 40 years ago, is tamoxifen - a SERM (selective estrogen receptor modulator). SERMs are a class of drugs acting directly on the estrogen receptor and have partial agonistic and antagonistic potential there. The drug was first tested in metastatic setting; later on, it was tested in the early setting where it lead to a reduction of relapse rate by 40-50% [18]. In premenopausal and postmenopausal females with low-risk breast cancer (small tumors, no effected lymph nodes), tamoxifen is still an important drug. It is also the best-studied drug for male breast cancer [19].

Another important drug family that was introduced to the clinic already almost 20 years ago - aromatase inhibitors, inhibiting the enzyme aromatase. Therefore, no active estrogens and estrogen metabolites are produced [20-23]. Aromatase inhibitor have demonstrated an advantage above tamoxifen in postmenopausal women, with higher response rates in the advanced setting, as well as an improved disease free survival in early breast cancer [24,25]. For high-risk breast cancers, combination of aromatase inhibitors with gnrh analogues are recommended in premenopausal women [26-28].

The duration of endocrine treatment in the adjuvant setting is still controversial. For a long time, the standard of care was 5 years [29]. More and more evidence show that a treatment of 10 years is better, providing an improved relapse free survival [30]. So far, no study showed a survival benefit for an extended treatment; thus, the patients should be advised carefully. Factors, which should be taken into account, are age, risk level, bone health and patients preference [30-32].

Recent investigations have lead to further improvements in the adjuvant breast cancer setting by the use of adjuvant bisphosphonates. The mechanism of preventing cancer cells from seeding to the bone is not completely understood, but solid hypothesis have been proposed [33-37]. These drugs have been studies extensively in the metastatic and adjuvant setting. In the adjuvant setting, a meta-analysis demonstrated a 2-3% survival benefit in postmenopausal patients [38-41]. Some data for premenopausal women with breast cancer are available [42-44]. The new St. Gallen Guidelines recommend bone targeting agents in the adjuvant setting, e.g. zoledronic acid 4 mg twice a year in postmenopausal breast cancer patients [45,46].

Endocrine therapy in advanced breast cancer

As of today, the prognosis of breast cancer is much better than it was decades ago. The relapse rate is less than 30%. In hormonal receptor positive breast cancer, there is a high proportion of late relapse after 5 years of endocrine therapy. In high-risk node positive hormonal receptor positive patients with more than three lymph nodes, the rate is up to 40%.

Tamoxifen was the gold standard in metastatic hormonal receptor positive breast cancer, as it provided a high clinical benefit rate and a progression free survival of around 6-12 months in the primary setting [47]. In premenopausal patients, the addition of gnrh agonists showed an additional advantage - an increased response rate and better overall survival [48]. Recurrence-free survival and overall survival are similar with gnrh agonist alone or in combination with tamoxifen with results from different chemotherapy protocols in hormone receptor positive breast cancer. Both agents seem to have an additional important benefit: protecting fertility. Adjuvant therapy with gnrh agonists and tamoxifen presumably preserves reproductive function in this specific patients' population [49,50].

Aromatase Inhibitors (AI) have been in clinical use for decades, showing better outcomes for postmenopausal and premenopausal patients with metastatic breast cancer.[25,32,51] [25,32,51]. They are also preferred in adjuvant setting since they are well tolerated [21]. However, the prevailing problem now in metastatic breast cancer is the development of endocrine resistance [15,16,52]. The research is strongly focusing on elucidating mechanisms of acquired and innate resistance [53]. Many patients taking AIs experience disease progression within 12-24 months. In 1st line endocrine therapy setting, the clinical benefit rate is around 60%. Subsequent lines have a clinical benefit rate of 40%, 24% and 16% [54]. AIs beyond the 3rd line are not beneficial in most patients and a switch to chemotherapy is recommended [19].

Several mechanisms are involved in the development of endocrine resistance [55]. One of them is the loss of steroidal receptors during disease progression [56]. A Swedish cohort study demonstrated an ER disconcordance of 14% and a PR disconcordance of 39%. The loss of steroidal receptor was associated with a threefold increase of death risk. Therefore, patients with recurrent disease should receive a biopsy in order to confirm tissue diagnosis and measure the expression of biomarkers, which then determinate the therapy course [9-13]. In the era of precision medicine and targeted management, it becomes more and more important to have fresh tissue to determine the best approach [57].

Treatment to overcome endocrine resistance in early and metastatic breast cancer

Clinically endocrine resistance can be divided into primary and secondary (acquired) type. Primary endocrine resistance is defined as a relapse less than 2 years after finishing adjuvant endocrine therapy or progression of disease within 6 months on endocrine therapy in metastatic setting. Secondary resistance is defined as a relapse less than 12 months after finishing endocrine therapy or progression later than 6 months on endocrine therapy for metastatic disease [58].

Number of approaches has been proposed to overcome the resistance. One of the strategy is to combine endocrine with targeted agents [17]. Here, several pathways and alterations in-

volved in breast cancer is being used - alterations and mutations in the ESR1 gene, coding for the estrogen receptors [59-61]. Some of ESR1 mutations are known and have been described [62,63]. In clinical practice, a class of drugs has been developed to overcome ESR1 mutations – the SERDs [64]. SERDs are selective estrogen receptor degradation drugs that are effective in patients after aromatase inhibitor or tamoxifen failure. Fulvestrand, the commonly known SERD, showed promising activity in the advanced endocrine resistant setting [65,66].

Some further resistance mechanisms are amplification and up-regulation of co-activators, as well as alterations in co repressors, e.g. AIB1, MNAR/PELP1 [67-69].

Promising targets are pathways with a cross-talk to the steroidal hormonal pathway. Most studied ones are alterations involving CDK4/6 proteins, PIK3CA, ESR1, CCND1, FGFR1, BRCA1, BRCA2, AKT1 and HER2 [70]. Several drug combinations are now under investigation.

Targeting the PIK3CA pathway seems to be effective, however most analysis are still experimental and look at a combination of factors, such as mTor inhibitors [71-73]. So far, pan-PI3K inhibitors, such as buparlisib, pictilisib and SAR245408, have not shown impressive efficacy, whereas PI3K-α-specific inhibition has shown more promise.

Everolimus - a mTor inhibitor - showed good outcomes in the endocrine resistance setting [74]. In a large trial with more than 700 patients priorly treated with chemotherapy, exemestane and 10 mg of everolimus, the combination treatment showed a prolonged progression free survival of 6 months. (4.1 vs. 10.6 months, HR 0.36, CI 0.27-0.47, p <0.001) Based on the trial results, the drug was approved by the FDA and EMA for patients with metastatic breast cancer that received previous treatment. Everolimus was also tested in combination of tamoxifen and fluvestrand, where it showed comparable benefit [75,76]. Trials are now investigating the drug in the adjuvant setting. (NCT01805271).

Targeting cycline depended kinase 4 and 6 (CDK 4/6) seems to be even more promising and three agents are meanwhile approved by the FDA: palbociclib, ribociclib and abemaciclib [77-79]. CDK4/6 are important regulators in the cell cycle. D-type cyclins are regulated by mitogenic stimuli, including activation of RTKs and steroidal receptors [80]. Activation of this pathway includes a formation of a complex of cycline d with CDK4/6. Cycline D is also regulated by several other pathways including NF-KB, PIK3CA/AKT, STATs, ER/PR/AR, MAPKs, WNT/beta-catenin. The complex of cycline d and CDK4/6 leads to a phosphorylation of retinoblastoma gene, gene transcription of E2F and an activation of the cell cycle [81].

Nowadays, there are three drugs approved with large phase III evidence: Ribiciclib (MONALEESA-Studies), palbociclib (PALOMA-Studies) and Abemaciclib (MONARCH-Studies) [82-87]. All studies showed benefit in the primary endocrine responsive situation and in resistant situation. All trials were randomized against standard of care endocrine therapy, e.g. aromatase inhibitor or fulvestrand. All trials showed significant equal hazard ratio of 0.5-0.6. The most common side effects included neutropenia, although neutropenic fever was rare with only 1-2% of all cases. Even thought the drugs are generally well tolerated, there are some small differences in toxicity profile. Most importantly however, that the combination of the new drugs promises an estimated time on endocrine treatment of more than 36 months before switching to a chemotherapy regime.

Conclusion

While hormone receptor positivity in breast cancer are cornerstone of treatment and endocrine therapies lead to massive improvements of the outcomes, new problems arise as we are facing endocrine resistance. Primary (innate) resistance has been known for a long time, but it was affecting a minority of patients. In opposite, a significant number of females develop secondary resistance in response to endocrine treatment. The mechanisms are not fully clear, but largely dependent on hormones and endocrine manipulation, as well as genetics. Understanding the molecular mechanisms of endocrine resistance is the basis to identify potential targets and develop drugs accordingly. Some of them have already been tested and approved. Future approaches might focus on combination approaches, since it is assumable that more than one pathway is responsible for resistances. Further research is needed and clinical trials crucial in order to elucidate the underlying processes, identify biomarkers of response and finally identify patients who can mostly benefit from individual therapeutic options to overcome endocrine resistance.

Tables

Table 1: demonstrated randomiezd phase II and III trials for CDK4/6 inhibitors palbociclib, ribociclib and abemaciclib.

Study	Treatment	Patients	Phase	N	Effect
PALOMA-1	Letrozol±Palbocichb	Endocrine sensitive	2	165	PFS 20 vs. 10 months, pr0.0004
PALOMA-2	LetrozoliPalbocickb	Endocrine sensitive	3	666	PFS 24 vs. 14 months p<0.00001
MONALEESA2	LetrozoltRibociclib	Endocrine sensitive	3	668	PFS not reached vs. 15 months p<0.00001
Monarch-3	NSAltAbemaciclib	Endocrine sensitive	3	493	KS not reached vs. 14.7 months 1)=0.000021
PALOMA•3	FaslodextPalbocKlib	Resistant to **AI**	3	521	PFS 9.2 vs. 3.8 months p<0.001
MONARCH-2	FaslodextAbemacichb	Resistant to AI	3	669	PFS 16.4 v 9.3 months p<0.01

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