Hormone Therapy in Breast Cancer

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Rezumat

Hormonoterapia în cancerul mamar

Hormonoterapia este obligatorie pentru toate pacientele cu neoplasm mamar cu receptori hormonal prezenți. Ea este activă atât în adjuvantă cât și în boala metastatică. Singurul tratament hormonal adjuvant activ în pre- și postmenopauză este Tamoxifen. Durata tratamentului adjuvant influențează intervalul liber de boală, riscul apariției unui neoplasm mamar controlateral cât și durata supraviețuirii. Inhibitorii de aromatază: Anastrozol, Letrozol, Exemestan se folosesc numai în post menopauză. În boala recurentă după sau în timpul tratamentului cu Tamoxifen se folosește Fulvestrant. Analogii LHRH se folosesc în premenopauză în adjuvantă în anumite condiții, uneori în cazul recurențelor. Aproximativ 50% din neoplasmele mamare cu receptori hormonal prezenți sunt sau devin rezistente la hormonoterapie. Molecule implicate în anumite căi de creștere celulară tumorală reversează rezistența la hormonoterapie (Palbociclib, Everolimus).

Cuvintele cheie: Tamoxifen, Anastrozol, Letrozol, Exemestan, Fulvestrant, Analogii LHRH, Palbociclib, Everolimus

Abstract

Hormonal therapy is mandatory for all patients with hormone-receptor-positive breast neoplasms. It is active both in adjuvant and metastatic disease. The only active adjuvant hormonal therapy in pre- and postmenopause is Tamoxifen. The adjuvant treatment duration influences disease-free survival, the risk of a contralateral breast cancer apparition and overall survival. The aromatase

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inhibitors: Anastrozol, Letrozol, Exemestan are only used in postmenopause. Fulvestrant is used in recurrent disease after or during treatment with Tamoxifen. LHRH analogues are used in premenopausal patients in adjuvantcy and sometimes in case of recurrences. Around 50% of hormone-receptor-positive breast neoplasms are or become resistant to hormone therapy. Some molecules involved in some tumour cellular growth pathways reverse the resistance to hormone therapy (Palbociclib, Everolimus).

Key words: Tamoxifen, Anastrozol, Letrozol, Exemestan, Fulvestrant, LHRH analogues, Palbociclib, Everolimus

Introduction

Breast cancer treatment includes local therapies: surgery, radiotherapy and systemic: chemotherapy, hormonal therapy, targeted therapy.

The choice of systemic therapy is made depending upon the recurrence risk established through the prognosis score for each patient.

DNA studies led to the identification of an "intrinsic list" of over 500 genes which define 5 biological subtypes of breast cancer: luminal A, luminal B Her2 -, luminal B Her2 +, Non luminal Her2+, basal-like.

Nowadays, there are several multigene prognostic tests commercially available: Oncotype Dx(21), Mamaprint, Heredigen. The test results assign a low, intermediate or high recurrence risk. In 2009, at the breast cancer conference in San Antonio, it was established that the prognostic score obtained through immunohistochemistry testing of ER, PR, Her2/neu and Ki67 (IHC 4) is concordant to those offered by the genetic tests. In everyday practice we use IHC 4.

The patients with a low recurrence score benefit from hormone therapy, while chemotherapy is mandatory for patients with high recurrence score. For patients having an inter-

mediate recurrence score, the systemic therapy chosen takes into account risk factors like: age, tumour size, tumour differentiation degree, the extension of lymph nodes invasion.

Intrinsic groups of breast cancer - *Table 1*.

The nuclear receptors for estrogens and progesterone have an important role for the growth and differentiation of the normal mammary gland epithelium, and their expression in breast cancer is the most important predictive factor of the therapeutic response. Also, into a smaller extent, it is a prognostic factor.

Her 2

Her 2 is a molecule involved in the cellular proliferation, present on the surface of normal mammary gland epithelium cells and over expressed by approximately 20% of breast cancers, which determines their genomic instability and excessive proliferation. Currently, Her2 expression is considered to be the most important prognostic factor in breast cancer.

We ought to mention BRCA1 and BRCA2, suppressor genes involved in cellular response to DNA alterations. The inherited mutations of these genes are associated to a high risk of

Table 1.

ER	+	+	+	-	-
PR	+>20%	<20%	anyway	-	-
Ki67	<20%	>20%	anyway	anyway	anyway
Her2/neu	-	-	+	+	-
	Luminal A like	Luminal B like Her 2 -	Luminal B like Her 2 +	Nonluminal Her +	Basal like

breast / ovary cancer emergence (1,2,3). Even if breast cancer associated to BRCA 1 mutation is most often triple negative, oophorectomy reduces the risk of breast cancer with 50% in the case of mutant BRCA1 bearers; chemoprevention with Tamoxifen in patients with BRCA1 and BRCA2 mutations and breast cancer reduces the risk of developing collateral breast cancer by 50% and enhances survival.

The hormonal treatment in breast cancer is addressed to patients whose tumours express hormone receptors (HR +), for estrogens (ER +), for progesterone (PR +), or for both. Hormonal therapy may be administrated in neoadjuvant, adjuvant and metastatic disease.

The inventor of hormone therapy, Sir Thomas Beatson, was a surgeon who in 1896 presented the data obtained on a series of patients with advanced breast cancer, noticing that survival had been better in patients who had had oophorectomy, and recommended this procedure as palliative care for advanced breast cancer.

The estrogen receptor, with the two isoforms α and β , has a role in developing normal mammary gland epithelium but also in developing a breast cancer (approximately 70% of breast cancers overexpress ER).

ER

ER is a nuclear transcription factor. ER α and ER β are coded by different genes. ER α is most frequently associated with breast cancer, with two transcription activating domains (AF).

Ligand (estrogen) + ER: polymerisation, activation of AF1, AF2 $\rightarrow$ intranuclear DNA $\rightarrow$ estrogen-dependent gene activation ER also has a zone which activates ligand-independent transcription, which determines "cross-talk" with others pathways of cellular proliferation after phosphorylation, like mTor.

PR

PR is coded by an estrogen-dependent gene.

The fluctuation of PR presence in breast cancer cells has a prognostic and predictive value (4); ER+, PR+ breast cancer has a better

response to antiestrogen therapy (50-70%) than the ER + PR- (30%).

Hormone Therapy

Hormonal therapy has the purpose of preventing the interaction between estrogens and estrogen-dependent pathways of stimulating neoplastic cells. It can be performed through:

1. Blocking the production of estrogens:
 - ovarian inhibition:
 - surgical (oophorectomy);
 - radiological;
 - chemical (LH-RH analogues);
 - aromatase inhibitors (conversion enzyme of androgens precursors in estrogens).
2. Blocking the estrogens action upon tumour cells:
 - SERM - act as estrogen agonists, antagonists or both, depending on the tisular target: Tamoxifen, Toremifen, Raloxifen;
 - SERD - inhibition of ER activity: fulvestrant, ER antagonist without estrogen agonist effects.

The LH-RH analogue used in current practice is goserelin 3,6 mg, intradermal at 28 days.

The aromatase inhibitors currently used are 3rd generation non-steroidal aromatase inhibitors (reversible): Anastrozol 1 mg/day p.o and Letrozol 2,5 mg/day p.o or steroidal (irreversible): Exemestan 25 mg/day p.o. Active only in postmenopausal patients. There is no crossed resistance between the two types of aromatase inhibitors.

Tamoxifen is the SERM the most used, active in pre and postmenopause in the dose of 20 mg/day p.o; the response to Tamoxifen varies depending on the ER and PR percent from the HR+ breast cancer cells. The benefit of Tamoxifen therapy continues after the termination of treatment (5) and is independent and additive to the benefit of chemotherapy. It acts as estrogen antagonist in HR+ breast cancer cells, partially estrogen agonist in endometrial cells and estrogen agonist in bone cells. Oxford Review (2005-5) of randomized clinical trials showed that the adjuvant therapy

with Tamoxifen for five years decreases the risk of recurrence by 41%, and the risk of death due to breast cancer by 34%, compared to non-Tamoxifen; at a follow-up after 15 years the mortality of patients who received 5-year treatment with Tamoxifen was by 30% lower than in patients who received a 2-year treatment with Tamoxifen. Also, 5 years of adjuvant therapy with Tamoxifen determined the decrease by 47% of collateral breast cancer risk. The benefit was proven for both patients with lymph nodes invasion (global survival at 10 years with 10% better than non-Tamoxifen) and without lymph nodes invasion (global survival at 10 years with 6% better).

The side effects of Tamoxifen treatment, which could limit to a certain extent its use, include the endometrium neoplasm, uterine sarcoma and the thromboembolic risk. A good monitoring of the treatment is mandatory: usually the gynaecologic examination, Babes-Papanicolaou citological examination, transvaginal U/S.

SERD Fulvestrant, an injectable antiestrogen is more active in postmenopause than in premenopause and it is indicated in the case of disease progression during or after Tamoxifen. Dosing schedule: 2 x 250 mg i.m monthly with an extra dose at 15 days in the first month.

Neoadjuvant hormone therapy is indicated in HR+ "low-grade" locally advanced breast cancer, or in patients with comorbidity / age which do not allow administration of chemotherapy.

Adjuvant hormone therapy is indicated in all patients with HR+ breast neoplasm. It is not recommended to be administered concomitant to chemotherapy, but it can be administered during radiotherapy. In premenopause it consists of Tamoxifen +/- surgical / chemical ovarian inhibition. Ovarian inhibition is efficient as compared to therapeutic abstention (6). It is equivalent to CMF chemotherapy and can replace it. It is also indicated for premenopausal patients who did not become amenorrheic after chemotherapy (7). It decreases the recurrence risk with 6% and the death risk due to breast cancer with 6.3%. Unlike surgical or radiological inhibition, the chemical ovarian inhibition is not definitive, which is an

advantage in young patients, whose fertility is preserved. For now, no clear benefit was proven for associating LH-RH analogues treatment to Tamoxifen in adjuvant disease, but according to the consensus in Lisbon (2011), it is recommended to use the association of LH-RH analogues in the first two years of treatment in patients under 35 years old with HR+ breast neoplasm, who undergo adjuvant treatment with Tamoxifen (the first two years represent the period with the highest incidence of local and/or distant recurrences in the natural history of a breast cancer). In post-menopausal patients, the adjuvant hormonal therapy is Tamoxifen or aromatase inhibitors (8). Adjuvant therapy with aromatase inhibitors is indicated from the beginning in "high risk" patients (for example Her2+, important lymph nodes invasion) or in patients with counterindication for Tamoxifen through comorbidity. There are studies which showed the benefit of adjuvant therapy in post-menopause with Tamoxifen 2-3 years, followed by Exemestan 3-2 years (9). Also, taking into consideration the long natural history of HR+ breast cancer, where recurrences often appear between years 6-15, there are clinical studies which showed the benefit of adjuvant treatment with an aromatase inhibitor for 5 years, after a 5-year period of Tamoxifen adjuvant treatment. (10)

According to the same consensus in Lisbon in 2011, in case of HR+ metastatic breast cancer hormonal therapy is "the first-line treatment even in case of visceral metastases if hormone therapy resistance is not suspected, or diseases progression is not too fast". Patients with HR+ metastatic cancer are eligible for hormone therapy if they had a significant on disease-free survival (DFS) and if they adjuvant hormonal therapy.

The purpose of the treatment is not curative, since metastatic breast cancer cannot be cured. In order to choose the optimal therapy the risk factors have to be evaluated:

1. disease risk factors:
 - disease-free survival (DFS);
 - previous treatments and the response to them;
 - biological factors (HR, Her2);

- tumour volume (the number and the site of metastases);
 - the necessity of a rapid control of symptoms.
2. patient risk factors:
- preference;
 - biological age;
 - menopausal status;
 - IP and comorbidity;
 - socio-economical and psychological factors;
 - available therapies.

In HR+ metastatic breast neoplasm all hormonal therapies seem to have equivalent efficacy. The duration of the first response to hormone therapy is 9-12 months. For eligible patients hormone therapy has to be administered sequentially (line 1, 2, 3), chemotherapy being recommended only if there is no response to hormone therapy.

Almost half of the patients with HR+ breast neoplasm have de novo or acquired resistance to hormone therapy, one of the resistance mechanisms to hormone therapy being the activation of mTor cellular pathway. S6 kinase beta-1, the substrate of mTor complex, phosphorylates the ligand-independent activator domain of ER. mTor Everolimus inhibitor blocks the reaction and can reverse the resistance to hormone therapy. Bolero 2 clinical trial proved that the association of Everolimus 10 mg/day p.o with Exemestan 25 mg/day p.o in patients with HR+, Her 2- metastatic breast cancer in progression under a nonsteroidal aromatase inhibitor doubles progression-free survival (PFS) compared to Exemestan alone.

Cyclin-dependent kinases 4 and 6, which regulate cellular growth and division are inhibited by Palbociclib. Clinical studies showed that hormone-naïve patients with HR+, Her2-advanced breast cancer who received Palbociclib 125 mg/day and Letrozol 2,5 mg/day, p.o had a PFS of 24.8 months as compared to 14.5 months for patients who received only Letrozol (Paloma 2), and patients with HR+, Her2 - metastatic breast neoplasm in progression under hormone

therapy who received Palbociclib plus Fulvestrant had a PFS of 11.2 months compared to 4.8 months in patients who received only Fulvestrant (Paloma 3).

The examples above show that targeted therapy can influence the response to hormonal therapy of patients with HR+ breast neoplasm.

Conclusion

In conclusion I would like to quote Professor Gabriel Hortobagyi from MD Anderson Cancer Center: "Breast cancer is a conglomerate of molecularly defined multiple syndromes, which are different as to their natural history, clinical evolution and sensitivity to external therapeutic agents".

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