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REVIEW

NEW AGENTS IN THE FIRST LINE TREATMENT OF METASTATIC OR LOCALLY ADVANCED ENDOCRINE POSITIVE, HER-2/NEU NEGATIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN. A REVIEW

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Abstract

Metastatic breast cancer (BC) has a poor prognosis, its treatment having a palliative intention. Owing to the development of new target agents, significant improvements in survival of metastatic BC appear. Similarly to non-metastatic BC, the management of metastatic BC depends on the expression of the hormone receptor (estrogen and/or progesterone) and the human epidermal growth factor 2 (Her-2/neu). As we know that estrogen hormones stimulate the development and progression of hormone-receptor positive BC, anti-estrogen therapies remain the most effective endocrine therapy, also in the metastatic setting, by reducing the estrogen production, antagonizing the receptor of estrogen or blocking the signal pathways through the estrogen receptor. However, in a subset of metastatic BCs in postmenopausal women and namely hormone positive, Her-2/neu negative BCs, a newly developed or acquired resistance to the endocrine therapy, reflected by a progression of the disease more than 12 months from the end of the adjuvant endocrine therapy, results in a reduction of the survival outcome

Résumé

Nouveaux agents dans le traitement de première ligne du cancer du sein métastatique ou localement avancé endocrinien positif, Her-2 / neu négatif chez les femmes ménopausées

En général, le cancer du sein métastatique (BC) a un mauvais pronostic, son traitement ayant une intention palliative. En raison du développement de nouveaux agents cibles, des améliorations significatives de survie de la BC metastatique surviennent. De façon similaire à la BC non metastatique, la prise en charge de la BC métastatique dépend de l'expression du récepteur hormonal (œstrogène et / ou progestérone) et du facteur de croissance épidermique 2 humain (Her-2/neu). Comme nous savons que les hormones oestrogènes stimulent le développement et la progression de la BC positive aux récepteurs hormonaux, les thérapies anti-oestrogènes restent la thérapie endocrinienne la plus efficace aussi dans le contexte métastatique en réduisant la production d'œstrogènes, en antagonisant le récepteur des œstrogènes ou en bloquant les voies

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respectively in a lower progression-free survival (PFS) rate. Moreover, the single use of the anti-hormonal agents, letrozol or anastrozole, in the first-line therapy, did not had a significant positive impact on the overall survival rate. On the basis of the low efficiency of hormonal agents, a new agent has been promoted in the initial anti-hormonal therapy of postmenopausal ER+/ Her-2/neu negative metastatic BC. It is the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor Palbociclib which, in combination with the aromatase-inhibitor Letrozole, resulted in a significant improvement of the PFS rate. In this paper we address the recent developments on the treatment of locally advanced or metastatic ER+, Her-2/neu negative metastatic BC, focusing on the combination of Palbociclib with Letrozole or Fulvestrant, in postmenopausal women.

Keywords: breast cancer, estrogen receptors, overall survival.

Abbreviations:
BC= breast cancer; ER=estrogen receptor; HER-2/neu= human epidermal growth factor; PFS= progression free survival; OS= overall survival; FDA= Food and Drug Administration

du signal par le récepteur d'oestrogène. Cependant, dans un sous-ensemble de BC métastatiques chez les femmes ménopausées et à savoir les hormones positives, les BC négatives Her-2/neu, une résistance nouvellement développée ou acquise à la thérapie endocrinienne reflétée par une progression de la maladie de plus de 12 mois à partir de la fin de la thérapie endocrine adjuvante entraîne une réduction du taux de survie respectivement dans un taux de survie sans progression (PFS) plus faible. En outre, l'utilisation unique des anti-hormonaux-letrozol ou anastrozole dans la thérapie de première ligne n'a pas eu un impact positif significatif sur le taux de survie globale. Sur la base de la faible efficacité des agents hormonaux, un nouvel agent a été promu dans la thérapie anti-hormonale initiale post-ménopausique ER +/ Her-2/ neu métastatique négative BC. Il s'agit de l'inhibiteur de la kinase 4/6 cycline-dépendante (CDK4/6) Palbociclib qui, en association avec l'inhibiteur de l'aromatase Letrozole, a entraîné une amélioration significative du taux de PFS. Dans le présent article, nous avons cherché à aborder les développements récents sur le traitement de localement avancé ou métastatique ER +, Her-2/neu métastatique négative BC en se concentrant sur la combinaison de Palbociclib Letrozole ou Fulvestrant chez les femmes post-ménopausées.

Mots-clés: cancer du sein, récepteurs aux œstrogènes, survie globale.

Introduction

According to actual guidelines, locally advanced or metastatic BC, which presents the expression of the estrogen and/or progesterone receptors (ER+ and/or PR+) and lack of the overexpression of the human epidermal growth factor 2 (Her 2/neu negative), are best treated with anti hormonal agents, with the aim to obtain a good control of the disease with no significant progression[1].The drugs used in the first-line treatment in postmenopausal women, Letrozole, Anastrozole or Fulvestrant, used as monotherapy or in combination, did not show a positive impact on the overall survival (OS) rate[2]. Moreover, many women present either de novo lesions or progressive disease under a certain endocrine therapy; due to these reasons, the scientists continued the research regarding other treatment combinations or alternatives of metastatic ER+/Her-2/ neu negative BC without extensive or extremely symptomatic metastases[3].

The researchers tried to develop new targeted molecules which, in combination with an anti hormonal agent, may provide better outcomes in terms of PFS and OS. In this way, for postmenopausal women with endocrine sensitive, Her-2/neu negative, locally advanced or metastatic BC, the current options include a monotherapy using an aromatase inhibitor or fulvestrant, or the combination of an aromatase inhibitor and a cyclin-dependent kinase inhibitor (CDK4/6)[4]. The latter agent, namely Palbociclib, has been approved in 2015 by the US Food and Drug Administration (FDA), based on the results of the multicentric trial PALOMA 1, showing that Palbociclib has the ability to reduce the resistance to the endocrine therapy while its combination with an aromatase inhibitor has resulted in a better PFS rate[5,6].

Favorable results have also been obtained with the combination of anastrozole and fulvestrant, which showed an improved OS rate[7]. However, the selection of the most suitable agents must take into consideration the clinical setting and the patient's comorbidities and preferences. In this review we emphasize the therapeutic benefit of the newly developed cyclin-inhibitor Palbociclib, used in combination with Letrozole, as intial endocrine therapy of ER+/Her-2 neu negative metastatic or locally advanced BC.

CDK4/6 inhibitors and Letrozole

The cyclin-dependent kinases are part of the threonine/serine kinases family and have an important role in the cell division, some of them playing a role in the pathogenesis of BC, more exactly in ER+ BCs. The expression of the hormone receptors inducts the expression of the cyclin D1 and CDK4/6 which, together with steroid or peptide growth factors, stimulates the proliferation of malignant cells and activate the phosphorylation of the tumor suppressor retinoblastoma 1 gene product (pRb)[8]. In this way, the malignant cell passes from the first growth phase G1 in the DNA synthesis phase S[4,9]. By inhibiting the formation of the cyclin D-CDK4/6 complexes, the cells will remain in the G1 phase, hence blocking the proliferation of BC[5,10]. However, the adverse effects, especially those from non-selective CDK4/6 inhibitors, are important: severe neutropenia, nausea, alopecia, cardiac or pulmonary dysfunction[11]. At present, there are three molecules CDK 4/6 inhibitors which have been studied in the setting of metastatic BC: ribociclib, abemaciclib and palbociclib, the latter being a highly selective inhibitor of the CDK4/6[12].

Based on the interactions between the cycline-dependent kinases in the cell cycle, it has been demonstrated that Palbociclib, orally administered, is the most effective in ER+, Her-2/neu negative BCs, by maintaining the cells into the G1 phase of the cell cycle[13]. Moreover the combination between Palbociclib and an aromatase inhibitor has a synergistic effect in inhibiting the proliferation of ER+ BC cells. This way, the efficiency of the combination between Palbociclib and Letrozole in postmenopausal women with advanced or metastatic ER+, Her-2/neu negative BC, has been confirmed in 2015 by the FDA[14]. The combination has showed a better PFS rate compared to Letrozole used as monotherapy, the results being extracted from the multicentric-randomized trial phase I/II –PALOMA I/II[14]. In this trial, 165 postmenopausal women with ER+, Her-2/neu negative advanced BC received, as first-line endocrine therapy, either Palbociclib-125 mg/d orally for 21 days followed by 7 days pause and Letrozole 2,5 mg/d continuously or Letrozole as monotherapy. The second phase of the trial divided the patients in two cohorts: biomarker-positive patients and biomarker-negative patients. The combination of Palbociclib and Letrozole resulted in a longer median PFS-20 months compared to the median PFS of 12 months after using Letrozole alone[15]. Furthermore, in the study of Finn et al[16], Palbociclib and Letrozole resulted in a median PFS of 24 months versus 14.5 months with Letrozole alone, while the responses rates were 42% and 35%, respectively. However, both the PALOMA II trial and the study of Finn et al did not demonstrate a significant impact of Palbociclib and Fulvestrant on the OS rate compared to Letrozole alone: 37.5 months versus 33.3 months, without significant improvement[13]. The above presented results were independent from age of the patients, grade of tumor differentiation, the presence of visceral metastases or prior adjuvant or neoadjuvant chemotherapy[17].

Adverse effects of Palbociclib and Letrozole

Although relatively well tolerated, the most common side effects of the combination Palbociclib and Letrozole were: neutropenia, leukopenia, fatigue and anemia. Neutropenia rates reached 75% in the PALOMA-1 trial and almost 85% in the PALOMA-3 trial. The pathogenesis of neutropenia is not clear, but it seems to be owed to the cytostatic effect on the progenitor cells. Febrile neutropenia has been reported in less than 1% of cases [18]. A grade 3 or 4 neutropenia is an indication either to stop the therapy or to reduce the dosage. Due to the side effects on the blood counts, a hemoleucogram is required before starting the therapy with Palbociclib, and after the first 2 cycles[19].

Ribociclib

Another CDK4/6 inhibitor which has been tested in combination with Letrozole and showed benefits is Ribociclib, a selective CDK4/6 inhibitor. With Ribociclib and Letrozole, a higher PFS rate has been registered in a phase III study conducted by Hortobagyi[20] and namely 63% compared to 42% for those who received only Letrozole. Favourable results were also observed regarding the response rate to the therapy: 41% versus 28%. The side effects of the combination Ribociclib and Letrozole included: neutropenia, leukopenia, grade 3 or 4 neutropenia and increased liver enzymes. However, severe side effects were observed in only 7.5 % of patients who interrupted the therapy with Ribociclib and Palbociclib[20].

Fulvestrant and Palbociclib

Fulvestrant is an antagonist of the estrogen receptor which blocks the function of the receptor before binding of the estrogen hormone to the receptor takes place[21]. It has been initially approved as monthly intramuscular injection of 250 mg, after an initial loading dose of 500 mg i.m on days 1, 14 and 29 in the first month. The use of higher doses proved to be more effective with a better median PFS and media OS[22]. The results were obtained in the FIRST trial[23] (First-Line Study Comparing Endocrine Treatments), a randomized phase II trial in which 205 women received either Fulvestrant 500 mg i.m monthly or Anastrozole 1 mg per os daily. Those who received Fulvestrant had a longer median PFS and median OS

than the group who received Anastrozole: 23 months compared to 13 months and 54 months compared to 48 months, respectively[23].

Taking into consideration the superiority of Fulvestrant over Anastrozole in the locally advanced or metastatic setting, the PALOMA 3 trial[24] tested the possibility to combine Palbociclib with Fulvestrant in postmenopausal women with ER+ and Her-2/neu negative advanced BC, who progresses after initial hormone therapy with an aromatase inhibitor. In the PALOMA-3 trial, 521 women have been randomized to receive either Palbociclib (125 mg/day orally for 21 days, followed by 7 days off) and Fulvestrant (500 mg intramuscularly every 14 days for the first three injections and then every 28 days) or Fulvestrant with placebo[18]. The study included also pre- and perimenopausal women who received Goserelin, together with Goserelin and Palbociclib. After a median follow-up period of 8.9 months, women who received Fulvestrant and Palbociclib had a better median PFS and namely 9.5 months compared to 4.6 months in the case of women who received Fulvestrant with placebo. Moreover, response rates were 10.4% with Fulvestrant and Palbociclib and 6.3% with Fulvestrant and Placebo[18]. On the other side, the combination of Fulvestrant and Palbociclib resulted in more side effects compared to Fulvestrant alone, in terms of neutropenia and fatigue syndrome. Febrile neutropenia appeared in less than 1% of cases[25]. However, the combination therapy didn't seem to affect the quality of life[26]. There is a limit of this study, especially with regard to the OS rate, which remains inconclusive owing to the short period of follow-up.

Other possibilities in the first line treatment

In postmenopausal women with metastatic BC, the aromatase inhibitors are the most efficient antihormonal agents as they have been proved to improve the OS rate when compared to Tamoxifen[27] or other endocrine agents combinations (e.g Exemestane and Anastrozole)[28]. Among all the aromatase inhibitors, Letrozole is considered to be the most efficient in inhibiting the aromatase enzyme although no clinically significant difference has been reported between different aromatase inhibitors[29].

The combination between an aromatase inhibitor – Anastrozole and Fulvestrant applied as a loading dose of 500 mg, then 250 mg on days 14 and 28, and 250 mg every 28 days, did not prove to be superior to the treatment with Anastrozole alone, resulting in similar median PFS and OS[30]. However, the Southwest Oncology Group (SWOG) S0226 trial showed that a higher dosis of Fulvestrant, 500 mg monthly, led to higher PFS and OS rates[31].

Conclusions

Palbociclib and antihormonal agents proved to be a better option compared to monotherapy endocrine therapy, in terms of median PFS in ER+, Her-2 neu negative, locally advanced or metastatic BC. Feasibility and clinical efficiency have been observed for Palbociclib and Letrozole or Palbociclib and Fulvestrant. The use of Palbociclib led to a prolonged (almost double) median PFS, which makes Palbociclib a feasible option in the metastatic or locally advanced setting, although the data on its impact on the OS rate are insufficient.

With regard to Fulvestrant, taking into consideration the results offered by the FIRST and PALOMA-3 trial, it can be concluded that Fulvestrant is a good alternative to Letrozole or Palbociclib and Letrozole in the first line treatment of ER+, Her-2/neu negative locally advanced or metastatic BC. Moreover, in combination with Palbociclib, it proved to bring benefits also in the second line therapy in women with hormone positive BC who progress after prior endocrine therapy in the metastatic setting. However, similarly to Palbociclib, its impact on the OS rate remains unclear.

The side effects of the CDK4/6 inhibitors with endocrine therapies include neutropenia and leukopenia, but no serious impairment of the patient's life quality has been reported. CDK4/6 inhibitors, together with Letrozole or Fulvestrant, proved to be a safe and feasible combination in a specific subset of patients. However, there are many questions that remain unanswered. One of these is the possibility to use this combination in early-stage BC as adjuvant treatment.

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