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Palbociclib + fulvestrant in a positive hormonal receptors metastatic breast cancer

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Summary

Palbocilcib is a first-in-class drug, that demonstrated in several studies, improvements in progression-free-survival, in combination with endocrine therapy. Palbociclib with fulvestrant improved progression-free survival in hormone receptor-positive, HER2-negative advanced breast cancer. The author reports the case of a 63-year-old metastatic breast cancer patient, positive for hormonal receptors, that had received multiple chemotherapy regimens. She was treated with palbociclib plus fulvestrant. Three months later she obtained partial response. However she also experienced side-effects such as grade IV neutropenia and grade III thrombopenia, that led to palbociclib reduction.

Key words: Palbociclib; Fulvestrant; Metastases; breast cancer; Positive hormonal receptors; Neutropenia; thrombopenia

Introduction

Growth of hormone-growth-receptor-positive breast cancer is dependent on cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), which promote progression from the G1 phase to the S phase of the cell cycle. Both CDK4 and CDK6 are among key proteins known to fuel the growth of hormone receptor-positive breast tumors.

The author reports the experience of a 63-year-old metastatic breast woman, treated with palbociclib, in association with fulvestrant.

Case Report

The author reports the case of a 63-year-old Caucasian woman, diagnosed with a left breast cancer in 2003. She had no medical past. She underwent mastectomy plus axillary lymph nodes removal. The histological findings showed a 1.8-cm invasive ductal carcinoma, without any vascular invasion, positive for estrogen receptors (80%) and progesterone receptors (50%), Her-2 negative, eight positive nodes out of 26 removed, and a pT1c N3a lesion.

The patient received six cycles of FEC (5FU, epirubicin, cyclophosphamide) adjuvant chemotherapy, followed by radiotherapy and hormonotherapy for five years. Eight years later, bone, mediastinal, liver, lungs, and cutaneous (scalp) metastases appeared. Biopsy of the scalp found breast metastases, positive for hormonal receptors (100% for estrogen receptors and 20% for progesterone receptors), and Her-2 negative. The patient began paclitaxel plus bevacizumab and denosumab therapy followed by bevacizumab plus exemestane for one year.

One year after first recurrence, multiple brain metastases appeared, while positron emission tomography scan did not show any extra cerebral metastases. The patient received in toto radiotherapy with carboplatin, followed by carboplatin plus pegylated doxorubicin chemotherapy for four months, then pegylated doxorubicin alone for four months. Eleven months after brain metastases, new progression (bones, brain, spleen, peritoneal, and subcutaneous) was diagnosed. The patient was treated with carboplatin plus navelbine, four courses delivered but without efficacy. She experimented four courses of eribulin without any response. She received one month of exemestane plus afinitor but the treatment was stopped because of grade IV dyspnea and pleural effusion. The patient then received six cycles of taxotere plus cyclophosphamide.

At disease progression it was decided to introduce palbociclib plus fulvestrant. The patient began with palbociclib at 125 mg per day, three weeks out of four. The fourth week the hemogram showed grade IV neutropenia, grade III thrombopenia, and grade II anemia that required three weeks to recover. Hepatic functions were normal. The positron emission tomography scan partial response with extinction of bone, splenic, and peritoneal metabolism. Ca 15-3 levels decreased from 101 to 77.3 KU/l (normal range < 25 kU/l).

The second cycle of palbociclib was administered at 100 mg/day. At the third week (day 17), grade I thrombopenia and grade II neutropenia appeared. The palbociclib was stopped until normal hemogram was achieved. Fulvestrant then followed.

Discussion

Palbociclib is an oral, small molecule, and a first-in-class inhibitor of cyclin-dependent kinase CDK 4 and CDK 6. In vitro, palbociclib reduced cellular proliferation of endocrine-receptors-positive breast cancer cell lines by blocking progression of cells from G1 into S phase of the cell

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cycle [1, 2].

In the phase II PALOMA-1 study, palbociclib plus letrozole significantly improved progression-free-survival, compared with letrozole alone, in patients with advanced estrogen receptor-positive breast cancer [3]. PALOMA-2 is a randomized double-blind phase III trial designed to confirm these results [4]. In the PALOMA-3, the phase III study, the combination of the CDK 4 and CDK 6 inhibitor palbociclib and fulvestrant was associated with significant improvements in progression-free-survival, compared with fulvestrant plus placebo in patients with metastatic breast cancer; irrespective of the degree of endocrine resistance, hormone receptor expression level, and PIK3CA mutational status [5].

The adverse events included disorders of the blood such as neutropenia, leukopenia, anemia, thrombocytopenia, fatigue, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, most of which were treatable.

The recommended dose and schedule of palbociclib is 125 mg daily for 21 consecutive days, followed by seven days off treatment. Palbocilcib is interesting and a promising drug because it allows to stall disease progression and stave off the need for chemotherapy for months.

Conclusion

Fulvestrant with palbociclib is more effective than fulvestrant alone for patients with advanced hormone receptors-positive breast cancer, but is more likely to cause neutropenia and thrombopenia. The combination could be considered as a therapeutic option for patients with recurrent hormone-receptor-positive, Her2- negative metastatic breast cancer that has progressed on previous endocrine therapy.

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