Palbociclib - A Novel Therapy for Hormone-receptor-positive Breast Cancer

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Abstract

Palbociclib has emerged as a novel inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). When activated by D-type cyclins, CDK4 and CDK6 phosphorylate proteins, the most important being retinoblastoma protein (RB1), which help to initiate the cellular transition from the G1 to the S phase. In hormone-receptor-positive breast cancer, cyclin D1 is overexpressed, thus driving the phosphorylation of RB1 by CDK4 and CDK6 and leading to increased cell proliferation. While most hormone-receptor-positive breast cancers are treated via endocrine therapy, some types are resistant to this treatment. Thus, by inhibiting CDK4 and CDK6 with extreme selectivity, palbociclib prevents the phosphorylation of RB1 and in turn arrests the cell in the G1 phase. In this research highlight, we will discuss a phase three trial paper from Turner *et al.* that assesses the efficacy of palbociclib, coupled with the estrogen receptor (ER) therapy fulvestrant, on patients with advanced hormone-receptor–positive, human epidermal growth factor receptor 2–negative breast cancer who had relapsed or progressed after being previously treated with endocrine therapy.

Keywords: palbociclib, hormone-receptor-positive breast cancer, cyclin dependent kinase, CDK 4, CDK 6, cyclin D1, fulvestrant, Phase 3 trial

Introduction

In a recent issue of the New England Journal of Medicine, Turner et al. present the results of a phase three trial of palbociclib coupled with fulvestrant.[1] When treating hormone-receptor-positive breast cancers, antiestrogen agents are often the first choice.[2] However, oftentimes resistance to antiestrogen agents develops over a period of time. This is especially apparent in the patients with progressive disease such as those chosen in this study.

Fulvestrant was chosen as a co-therapy because many patients had initially been receptive to antiestrogen therapy. Thus, an alternative estrogen receptor (ER) therapy, such as fulvestrant, was likely also be effective. Fulvestrant expresses its antitumor activity by preventing the binding of endogenous estrogens to estrogen receptor (ER). This stifles the estrogen-regulated gene transcription pathways that drive the proliferation of the cancer cells in question. The advantage of fulvestrant to antiestrogen therapies is that it has no known estrogen agonist activity. It simply blocks the estrogen receptor.

Palbociclib, on the other hand, offers a novel way of dealing with hormone-receptor-positive breast cancer. Rather than affecting the levels of estrogen hormones or blocking an estrogen receptor, palbociclib inhibits CDK4 and CDK6, preventing the phosphorylation of RB1 and arresting the cell in the G1 phase. In these cancers, cyclin D1, which activates CDK4 and CDK6 is heavily overexpressed. Thus, palbociclib can

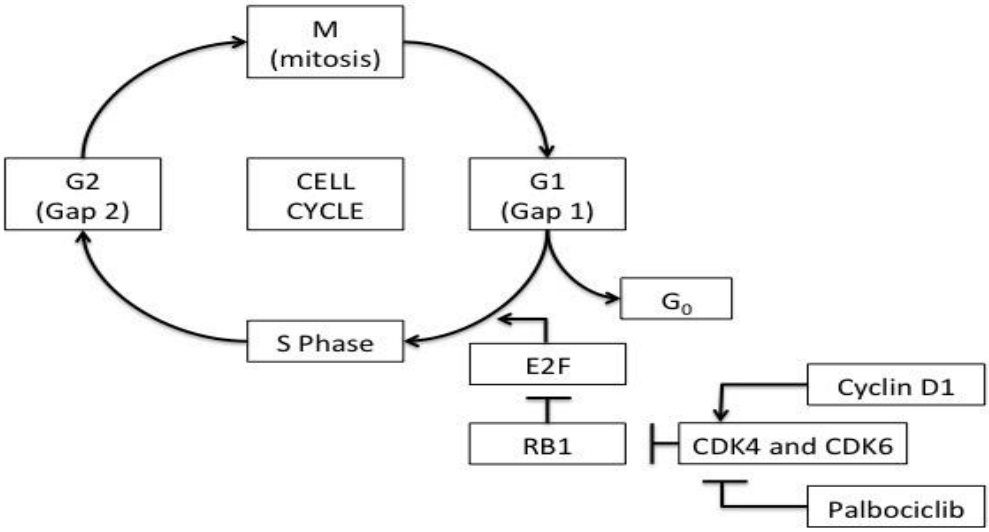

Figure 1. Scheme of Palbociclib's action, arresting the cell in the G1 Phase.

effectively reduce the increased proliferation normally triggered by the rise in cyclin D1 levels, arresting cells in the G1 phase so that they can no longer proliferate (Fig.1).

Authors' Results

The researchers set out to determine the effectiveness of palbociclib in conjunction with fulvestrant. This effectiveness was measured via progression-free survival. This metric was determined according to the RECIST guidelines. This guideline provides a predicted probability of progression-free survival based on tumor size, development of new lesions over time, and overall tumor burden (or lesions per organ), among other factors.[3]

Patients in this phase 3 trial were those who had advanced hormone-receptor–positive, human epidermal growth factor receptor 2–negative breast cancer. While it would have been relevant, patients were not screened for levels of CDK4 or CDK6 expression. The experiment was double blind, and a total of 521 patients were assigned to receive either palbociclib (125 mg per day orally for 3 weeks, followed by 1 week off) and fulvestrant (500 mg intramuscularly per standard of care every 14 days for the first three injections and then every 28 days) or placebo and fulvestrant. For those who received the placebo and fulvestrant, the median progression free survival time was 3.8 months. This pales in comparison to those who received the combination of palbociclib and fulvestrant, whose median progression free survival time was 9.2 months. The researchers did not, however, stratify the patient groups based on CDK4 or CDK6 expression. This information may be important going forward as it is possible that patients with higher levels of expression of these kinases may respond

to treatment differently from those who have lower levels.

However, side effects were reported in the palbociclib group that did not appear in the placebo and fulvestrant group. These adverse events included increased rates of neutropenia, leukopenia, fatigue and nausea. Neutropenia was the highest reported side effect across the board in the palbociclib and fulvestrant group. Yet, a very low incidence of febrile neutropenia was reported. However, global quality of life, including a significant improvement of emotional functioning, was shown in the palbociclib and fulvestrant group when compared to patients receiving placebo. Thus, the increased quality of life coupled with the longer progression free survival time point to palbociclib as an effective treatment for patients with advanced hormone-receptor-positive, HER-2 negative disease.

Conclusions

According to this study, palbociclib, in conjunction with fulvestrant, was proven to increase the progression-free survival time of patients when compared to patients who receive placebo and fulvestrant alone. Furthermore, the combination of palbociclib and fulvestrant increased the quality of life of patients with disease. This alone makes palbociclib a valuable tool in the fight against advanced forms of breast cancers where other traditional therapies have failed even though it was not able to consistently cure patients of disease as a sole therapy. Following the success of this phase 3 trial, the U.S. Food and Drug Administration has granted accelerated approval to palbociclib, under the name Ibrance, to treat advanced (metastatic) breast cancer. While it may be helpful to look at CDK4 and CDK6 expressions in each patient to see what effect expression has on efficacy, it is clear that putting this drug on the fast track to approval was appropriate and more data regarding its efficacy is sure to follow in the coming months.

References

1. Turner N, Ro J, André F, Loi S, Verma S, Iwata H, Harbeck N, Liobl S, et al. Palbociclib in Hormone-Receptor-Positve Advanced Breast Cancer. N Engl J Med 2015 373(3): 209-19. http://dx.doi.org/10.1056/NEJMoa1505270 PMid:26030518

2. McKeage K, Curran MP, Plosker GL. Fulvestrant: a review of its use in hormone rceptor-positive metastatic breast cancer in postmenopausal women with diesase pregression following antiestrogen therapy. Drugs 2004 64(6): 633-48. http://dx.doi.org/10.2165/00003495-200464060-00009 PMid:15018596

3. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009 45(2): 228-47. http://dx.doi.org/10.1016/j.ejca.2008.10.026 PMid:19097774