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# Safety and Efficacy of Palbociclib in Male Metastatic Breast Cancer: A Report of Two Cases

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## Abstract

Male breast cancer is uncommon. Most of the information regarding the treatment of male breast cancer patients are from retrospective studies. The treatment options are usually guided by the extrapolation of data from female breast cancer patients. Although it has been encouraged to include males in clinical trials of breast cancer treatment, the rarity of male breast cancer makes it difficult to enroll them in clinical trials. Therefore, real-world data related to male breast cancer is crucial to support the efficacy and safety of newly developed therapies. In the pivotal clinical trials for female patients with hormone receptor-positive and human epidermal growth factor receptor 2 -negative breast cancer, palbociclib (cyclin-dependent kinases 4 and 6 inhibitor) combined with endocrine therapy (ET) significantly increased the median progression-free survival as compared to ET alone. To our knowledge, this is the first case report to evaluate the efficacy and safety of palbociclib combined with ET in males with metastatic breast cancer in Japan.

We experienced two advanced male breast cancer successfully treated with palbociclib and endocrine therapy. Safety and efficacy was similar with those with female breast cancer.

**Keywords:** Male breast cancer, Palbociclib, CDK4/6 inhibitor, Letrozole, Fulvestrant

## Introduction

Male breast cancer accounts for approximately 0.7% of all breast cancer cases in Japan [1]. Compared to females, males are generally diagnosed at an older age (approximately 5 to 10 years older than women) [2]. Moreover, in most cases, breast cancer in males is generally diagnosed at an early clinical stage [3]. Although the breast cancer tissues from both males and females are macroscopically indistinguishable, they are histologically different. Whereas almost all male breast cancers are ductal in origin, those of lobular origin are very uncommon because male breast tissues lack acini and lobules [4]. Immunohistochemistry (IHC) suggests that male breast cancer is exclusively hormone receptor (HR)-positive, very rarely express human epidermal growth factor receptor 2 (HER2), and is rarely triple-negative [4,5]. The treatment approach to male metastatic breast cancer (MBC) is almost the same as that in women except for some points and the systemic therapy includes hormone therapy (HT) with tamoxifen, luteinizing hormone-releasing hormone (LH-RH) agonists, and aromatase inhibitors (AIs) [6]. Palbociclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6), which are activated by D-type cyclins. CDK4/6, which promotes cell-cycle entry by phosphorylating retinoblastoma protein and initiates the G1-to-S phase transition, are highly active in HR-positive breast cancer cell lines. Palbociclib has been shown to work synergistically with endocrine therapy (ET) [7,8]. In the PALOMA-1 clinical study, palbociclib combined with letrozole significantly increased the median progression free survival (PFS; 20.2 months) as compared to letrozole alone (10.2 months) in females with advanced HR-positive and HER2-negative MBC [9,10]. Subsequent randomized controlled trials proved that palbociclib combined with ET resulted in a significantly longer PFS than ET alone; however, only female patients were enrolled in these trials [11].

U.S. federal drug administration (FDA) and Japanese Pharmaceuticals and Medical Devices Agency originally approved palbociclib for female breast cancer treatment [12]. Subsequently, FDA expanded the approval of palbociclib to men based on real-world data (RWD) from electronic health records and insurance claims, which included studies on male MBC treated with palbociclib in combination with ET in April 2019 [13,14]. Here, we report two cases of HR-positive and HER2-negative male MBC treated with palbociclib combined with two different ETs.

## Case Reports

### Case No. 1

A 53-year-old man with stage IIB left breast cancer was treated with twelve doses of weekly paclitaxel as neoadjuvant chemotherapy followed by left-side total mastectomy with axillary lymph nodes dissection. Pathological findings revealed invasive ductal carcinoma (IDC), a primary tumor of size 22 mm, and 11 metastatic lymph nodes out of 14 resected nodes. IHC evaluation showed that the tumor cells were HER2 negative, while >70% of the cells were positive for estrogen receptor (ER), 30-70% were positive for progesterone receptor (PgR), and 5-19% were positive for Ki-67 expression. Tamoxifen was initiated as adjuvant ET, concomitantly with post-mastectomy radiation therapy (RT) with 50 Gy/25 fr. After two months of treatment, metastatic skin lesions emerged on his chest. Tamoxifen was then replaced with letrozole. After three months of letrozole treatment, new metastatic skin lesions emerged on his left upper back. Although high-dose toremifene was initiated and the disease stabilized for eight months, a positron emission tomography (PET)/computed tomography (CT) scan indicated metastasis to the sternum bone, based on which we evaluated the disease as being progressive. At this point, he was referred to our institution. We initiated palbociclib 125 mg p.o. once daily for 3 weeks during the 4-week cycle combined with fulvestrant 500 mg i.m. on days 1, 15, 29, and once monthly thereafter. During the first cycle of the treatment, grade 3 neutropenia according to the Common Terminology Criteria for Adverse Events version 5.0 occurred as an adverse event (AE). We reduced the palbociclib dose to 100 mg. The overall response was stable disease. At present, the patient is on palbociclib combined with fulvestrant for more than nine months without disease progression or serious AEs.

### Case No. 2

An 82-year-old man was diagnosed with right breast cancer at a hospital 22 years before referral to our department. He underwent mastectomy with axillary lymph node dissection, and pathological evaluation revealed IDC in the primary tumor and axillary lymph nodes. IHC evaluation indicated that the tumor cells were HER2-negative while >95% of the cells were ER-positive, 80% were PgR positive, and 5% were Ki-67 positive. He was followed-up without any adjuvant treatment for two years. During regular examination, local recurrence of the right breast cancer was observed. Tumorectomy with axillary lymph nodes dissection was performed combined with postoperative RT. He had been recurrence free for sixteen years before referral to our hospital. He visited the hospital with a complaint of newly occurred hoarseness, and a CT scan showed metastatic enlarged mediastinal lymph nodes. At this point, he was referred to our institution due to a suspicion of disease progression. On the first visit to our hospital, we followed the re-staging procedure and found metastatic enlarged cervical and axillary lymph nodes and a newly appeared thyroid mass. We obtained biopsies from the enlarged lymph nodes and the thyroid mass. Pathological evaluation revealed metastatic breast cancer and thyroid papillary carcinoma was suspected. We decided to prioritize the treatment for recurrent breast cancer and started tamoxifen as first line ET. He showed good response to tamoxifen treatment for one and a half year; however, CT scan indicated disease progression. Subsequently, he was switched to palbociclib 125 mg p.o. once daily for 3 weeks in a 4-week cycle combined with letrozole 2.5 mg p.o. once daily as second-line therapy. Since he experienced grade 3 neutropenia and thrombocytopenia in the first cycle, the second cycle with palbociclib 100 mg was delayed by one week. The overall response was a partial response. He continues to be on palbociclib combined with letrozole for more than one year and eight months without disease progression or serious AEs.

## Discussion

We reported two cases of male breast cancer that were successfully treated with palbociclib combined with ET. The estimated incidence new cases of male breast cancer, which is very rare compared to female breast cancer, was approximately 1% of all breast cancer cases diagnosed in 2019 [15].

The most common subtype of male breast cancer is HR-positive and HER2-negative. The treatment options are determined by extrapolating data on the same subtype of female breast cancer [3]. Palbociclib, an inhibitor of CDK4/6, is approved for the treatment of HR-positive MBC. Palbociclib combined with fulvestrant prevented disease progression after ETs in the PALOMA-3 study or can be combined with AIs for initial ET based on the PALOMA-1 and -2 studies in postmenopausal women [16]. The most common AEs (incidence ≥10%) associated with palbociclib treatment were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, and pyrexia [12]. In our report, although both the patients experienced grade 3 neutropenia and one of the patients developed grade 3 thrombocytopenia, the treatment was continued safely by reducing the palbociclib dose. In the PALOMA-3 study, approximately one-third of the patients who received palbociclib combined with fulvestrant continued with their treatment for more than two years [17]. Palbociclib combined with letrozole might show better outcomes in most of the endocrine-resistant HR-positive and HER2-negative patients, even if they have received multiple prior therapies for MBC in the expanded access program [18]. Based primarily on the PALOMA-2 and -3 studies and supportively on RWD from the electronic health records and insurance claims of male MBC patients, FDA recently expanded the palbociclib indication to include males [14]. As for the safety evaluation in male patients, FDA reviewed and supported the global safety database, two phase 1 clinical trials of palbociclib in male patients with other solid tumors, post-marketing reports on palbociclib, and a literature search. FDA rationally proved that the palbociclib-induced AEs in males were similar to those known in females [14]. We also did not observe any palbociclib-induced AEs that were specific for male patients. Due to the rarity of the disease, although male breast cancer patients are historically excluded from breast cancer clinical trials and there are only a few clinical case reports of male MBC treated with palbociclib [19], current clinical practice generally follows treatment guidelines for female breast cancers. Altogether, we encountered two cases of male MBC that benefited from palbociclib without serious AEs. Through this clinical experience, we recommend palbociclib for male MBC. We also recommend enrolling not only females but also males in future trials for breast cancer to collect data and develop prompt and efficient treatment strategies.

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