[¹⁸F]-Fluorodeoxyglucose Positron Emission Tomography/CT to Assess the Early Metabolic Response in Patients with Hormone Receptor-Positive HER2-Negative Metastasized Breast Cancer Treated with Cyclin-Dependent 4/6 Kinase Inhibitors

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Keywords

Breast cancer · Cyclin-dependent 4/6 kinase therapy · [¹⁸F]-fluorodeoxyglucose positron emission tomography-PET early metabolic response

Abstract

Introduction: Addition of cyclin-dependent 4/6 kinase (CDK4/6) inhibitors to endocrine therapy is standard of care in the treatment of women with advanced hormone receptor-positive HER2-negative breast cancer. However, the predictive factors for the treatment response to CDK4/6 inhibitor therapy are poorly elucidated. Early changes in the by [¹⁸F]-fluorodeoxyglucose positron emission tomography (FDG-PET) uptake of tumors receiving different kinds of therapy have proven to reliably predict treatment outcomes in a variety of malignancies. Therefore, the feasibility of early metabolic response assessment to predict the long-term treatment response to CDK4/6 inhibitor therapy was evaluated in the present study. **Methods:** Eight patients underwent FDG-PET/CT before and after the initiation of CDK4/6 inhibitor therapy (ribociclib, palbociclib or abemciclib). CDK4/6 inhibitor therapy was combined with either aromatase inhibition or fulvestrant. The median interval between

the treatment start (including baseline PET) and the follow-up PET examination was 14 days. Conventional radiographic staging was performed 3 months after the start of CDK4/6 inhibitor therapy. The percentual changes in molecular tumor volume, SUV_{peak}, the summed SUV_{peak} of up to 5 metastases (PERCIST-5), and total lesion glycolysis (TLG) were calculated for each patient. **Results:** Three patients showed progressive disease after 3 months of CDK4/6 inhibitor therapy, whereas 5 patients showed disease control (3 stable disease and 2 partial remission). Disease control was maintained in these patients (follow-up range 7–22 months). Patients with disease control had a significantly greater decline in TLG (–55.3 vs. 16.7%; $p < 0.05$). The same was true for the PERCIST-5 (–21.9 vs. 11.3%, $p < 0.05$). All patients with progressive TLG showed treatment failure and/or a poor outcome. **Conclusion:** Elevated TLG on early FDG-PET seems to be associated with long-term treatment failure and a poor outcome in patients undergoing CDK4/6 inhibitor therapy for metastatic breast cancer. Early findings indicate a potential prognostic value of early FDG-PET in this setting and warrant a prospective evaluation.

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Introduction

Breast cancer is the most common malignancy in women and a leading cause of cancer-related death [1]. Breast cancer is subtyped according to various histological features like the presence of estrogen receptor (ER) and progesterone receptor (PR). If these receptors are expressed, the application of endocrine treatment options like GnRH analogs, ER blockers, or aromatase inhibitors may prevent tumor progression. Among other effects, endocrine therapy prevents the expression of cyclin D, a protein that promotes progression in the cell cycle [2]. However, resistance to endocrine therapy is frequent, especially in advanced breast cancer [3]. Using a different mode of action, cyclin-dependent 4/6 kinase (CDK4/6) inhibitors prevent cancer cells from progression through the cell cycle, which has proven to be an effective strategy in hormone receptor (HR)-positive HER2-negative breast cancer [2].

Treatment with CDK4/6 inhibitors significantly prolonged progression-free and overall survival in HR-positive HER2-negative breast cancer patients in multiple randomized trials, including the MONALEESA-7, MONARCH, and PALOMA trials [4–9]. However, it remains unclear which patients will benefit from CDK4/6 inhibitor therapy. Predicting the response to CDK4/6 inhibitor therapy is of great importance given the high rate of side effects like neutropenia, diarrhea, and alopecia, the high treatment costs, and the possibility of initiating alternative therapy at an early time point [10].

Early metabolic changes assessed by [¹⁸F]-fluorodeoxyglucose positron emission tomography (FDG-PET) have been proven to predict the response and prognosticate outcomes in solid malignancies [11–13]. Therefore, the aim of this study was to investigate whether early metabolic changes in FDG-PET biomarkers might predict the response to CDK 4/6 inhibitor therapy and the outcomes of breast cancer patients. To this end, FDG-PET was performed before and after the start of CDK 4/6 inhibitor therapy, and metabolic changes were correlated with the 3-month response and outcome of the patients.

Methods

Patients

All patients with HR-positive HER2-negative metastasized breast cancer who underwent an FDG-PET examination before and after the start of CDK4/6 inhibitor therapy in the Department of Medical Oncology, University Hospital Essen, Essen, Germany, and the oncology outpatient clinic in Ravensburg were included in this analysis. Eight patients received an FDG-PET before and after the initiation of CDK 4/6 inhibitor therapy and were included in this analysis.

PET Acquisition

FDG administration and PET imaging were performed according to EANM guidelines [14]. Siemens Biograph mCT PET scanners were used for image acquisition (Siemens Healthineers, Knoxville, TN, USA). PET images were acquired before and after the start of CDK4/6 inhibitor therapy, and the median interval between the 2 PET acquisitions was 14 days (range 13–16).

Image Analysis

PET image analysis was done using a Siemens software research prototype (MIIIS; Siemens Medical Solutions USA, Inc., Knoxville, TN, USA). All lesions with an SUV_{peak} exceeding a liver-specific threshold were segmented ($2 \times \text{mean } SUV_{blood} + 2 \times SD \text{ } SUV_{blood}$). Foci with less SUV were added manually, if necessary. The metabolic tumor volume (MTV) was quantified using a 50% threshold of the SUV_{max} of the lesion. The total lesion glycolysis (TLG) was the product of the MTV and the mean SUV of each lesion. For the per patient PET uptake analysis, the maximal SUV_{max} and maximal SUV_{peak} were noted. For the per patient analysis of MTV and TLG, the sum of all of the lesions was calculated to obtain whole-body MTV and whole-body TLG. For the PERCIST analysis, the SUV_{peak} of up to 5 of the hottest lesions per patient (maximum 2 lesions per organ system) was summed and the result denoted PERCIST-5.

Response Assessment

CT response assessment was initiated 3 months after the start of CDK4/6 inhibitor therapy treatment. Depending on the result, scans were classified as progressive disease (PD), stable disease (SD), or partial response (PR). In addition to the CT graphic response assessment, clinical follow-up time and, if applicable, time until death were employed as endpoints.

Statistical Analysis

The percentual change of the pre- and posttreatment measurements was calculated for each parameter (SUV_{max} , SUV_{peak} , PERCIST-5, MTV, and TLG). R was used for waterfall and swimmer plot visualization as well as for Mann-Whitney U tests [15].

Results

Patient Characteristics

The patient characteristics are shown in Table 1. All of the patients received a combination of aromatase inhibitor or fulvestrant and a CDK4/6 inhibitor. Five patients showed CT graphic and clinically stable ($n = 3$) or partially regressive disease ($n = 2$), which was rated as disease control (non-PD). Three patients had clinically and CT graphic PD. The early metabolic response of 2 exemplary patients is shown in Figure 1.

FDG-PET Uptake Parameters

The PERCIST-5 reduction was significantly greater in patients with PD compared to those without (11.3 vs. –21.9%; $p < 0.05$). All patients with progressive PERCIST-5 had PD, whereas all patients with regressive PERCIST-5 had non-PD (Fig. 2).

The distinction between PD, SD, and regressive disease according to PERCIST was not judged by the PER-

Table 1. Patient characteristics

Patient No.	1	2	3	4	5	6	7	8
Age, years	64	56	50	59	40	37	63	72
CDK4/6 inhibitor	Pal	Pal	Pal	Pal	Pal	Pal	Ab	Rib
CDK4/6 inhibitor combination	AI	AI	Ful	AI	Ful	AI	Ful	AI
Primary tumor								
ER	+	+	+	+	+	+	+	+
PR	+	+	+	+	+	+	+	+
HER2 neu	–	–	–	–	–	–	–	–
Metastasis location								
Bone	Yes	Yes		Yes	Yes			Yes
Lymph node	Yes							Yes
Liver	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Lung					Yes			Yes
CDK4/6 inhibitor treatment in metastatic breast cancer								
First line	Yes			Yes		Yes	Yes	Yes
Second line		Yes	Yes		Yes			

PAL, palbociclib; Ab, abemaciclib; Rib, ribociclib; AI, aromatase inhibitor; Ful, fulvestrant.

Table 2. Initial FDG-PET measurements and response

Patient No.	Response	PERCIST-5 response, %	MTV response, %	SUV _{peak} response, %	TLG response, %	SUV _{max} response, %
1	SD	–4	–77	35.1	–73	11
2	PD	6	4	6.5	17	10
3	SD	–10	1	–4.2	–9	–14
4	PD	17	9	7.1	27	7
5	PD	11	9	0.7	12	7
6	SD	–53	–7	–50.9	–55	–49
7	PR	–23	–41	–23.0	–49	–24
8	PR	–37	–53	–20.8	–57	–60

CIST-5 but by comparing the maximum SUV_{peak} between baseline and the follow-up examination. Interestingly, only 1 patient (patient 1) was rated progressive according to PERCIST, whereas this patient had non-PD. Seven patients were rated as stable according to PERCIST, and this included 2 patients who had PD. Similar results were seen for SUV_{max} (Table 2).

FDG-PET Tumor Volume

The MTV decline was significantly less in patients with PD compared to those without (8 vs. –40.9%; $p < 0.05$). In fact, all patients who had PD had progressive MTV; however, 1 patient (patient 3) had mildly progressive MTV as well but was rated non-PD. Regarding TLG, all patients with regressive measurements were non-PD, whereas patients with PD had progressive TLG (Table 2). Patients with PD had a significantly smaller TLG decline compared to non-PD patients (16.7 vs. –55.3%; $p < 0.05$; Fig. 3).

Discussion

Early changes in FDG-PET uptake within an interval of 2 weeks seem to predict treatment failure of CDK4/6 inhibitor therapy in patients with metastasized breast cancer. Especially progressive TLG and manual PERCIST-5 measurements were found in patients with later confirmed radiographic progression and a poor outcome.

Currently there is no tool for early response assessment in patients with metastasized breast cancer undergoing CDK4/6 inhibitor therapy. Depending on the treatment line and the presence of visceral metastasis or endocrine resistance, the median PFS is <10 months, with up to 40% of patients having PD during the first 6 months of treatment [10, 16]. Moreover, CDK4/6 inhibitor therapy causes significant adverse reactions and high treatment costs, making early response assessment an important clinical issue. In addition, early treatment modifications in nonresponding patients might result in better out-

Fig. 1. A Patient with no early metabolic response (patient 2; 13 days between PET examinations). **B** Patient with an early treatment response to CDK4/6 inhibitor therapy start (patient 7; 14 days between PET examinations).

Fig. 2. Waterfall plot of all of the patients. Waterfall plots of the relative changes in SUV_{max} (A), PERCIST-5 (B), TLG (C), and MTV (D) after CDK4/6 inhibitor therapy start are shown. PD vs. non-PD classification is based on CT graphic assessment 3 months after the initiation of CDK4/6 inhibitor therapy.

comes – a strategy that is being tested in ongoing phase 3 trials such as the PADA-1 trial [17].

Large efforts have been made to characterize molecular biomarkers correlated with resistance to or benefit from CDK4/6 inhibitors [18]. However, genomic alterations or protein expression of a large array of genes involved in cell cycle regulation or signal transduction have failed to detect a biomarker able to robustly select patients without benefit from CDK4/6 inhibitors [10]. Therefore, the clinician has to await the first conventional staging to assess the efficacy of CDK4/6 inhibitor treatment. Conventional staging usually is performed months after the initiation of CDK4/6 inhibitor therapy, which prevents early treatment optimization. It was shown in this study that very early changes in metabolic tumor biomarkers can identify patients at risk of treatment failure within days after the initiation of CDK4/6 inhibitor therapy.

This offers the possibility of early treatment intensification or a change of treatment strategy in patients with treatment failure.

In the present preliminary study, early progression of FDG-PET measurements was found in patients with a poor outcome. This is in line with previously published studies in other cancers evaluating very early changes in FDG uptake to detect treatment failure. For example, the MUNICON trial elucidated whether patients with distal esophageal adenocarcinoma or gastric cardiac adenocarcinoma showed a metabolic response within 14 days after the start of chemotherapy [13]. Similar results were shown for breast cancer patients in the AVATAXHER trial [19]. If a metabolic response was present, chemotherapy was continued. Otherwise, early surgical resection was intended. Nonresponding patients showed a poorer outcome. In another trial, an absent very early metabolic re-

Fig. 3. Swimmer plot of all of the patients since the start of CDK4/6 inhibitor therapy. Censored patients are marked by an arrow, and deceased patients are marked by a cross. Patients were separated by TLG change into progressive TLG and regressive TLG.

sponse in breast cancer patients receiving buparlisib was associated with PD [20]. These trials corroborate our finding that repetition of FDG-PET within 14 days to observe the very early metabolic response can facilitate the detection of treatment failure.

Among the evaluated parameters, PERCIST-5, TLG, and MTV could potentially identify patients at risk of treatment failure. TLG is a surrogate for the glucose uptake of a tumor lesion. MTV is a surrogate of the glucose avid tumor volume. The PERCIST score is the sum of the SUV_{peak} of the 5 hottest lesions (maximum 2 per organ system) and thereby measures the maximum glucose uptake in the tumor. It seems plausible that the reduction of glucose metabolism, for which these PET metrics are surrogate parameters, is correlated with the long-term radiographic treatment response.

Previous publications have analyzed the metabolic response in breast cancer patients. Keam et al. [21] showed that the early metabolic response could predict the histopathological response to neoadjuvant chemotherapy in breast cancer. In addition, Sabet et al. [22] demonstrated that metabolic changes measured by FDG-PET could prognosticate the outcome of patients with breast cancer and liver metastases treated by radioembolization.

A recent study by Taralli et al. [23] employed FDG-PET to assess the response of breast cancer patients to CDK4/6 inhibitor therapy. In contrast to the present study, Taralli et al. [23] did not investigate early treatment changes as the interval CDK4/6 inhibitor treatment start and follow-up PET was 143 days (median), whereas the interval between baseline and the follow-up PET after the start of CDK4/6 inhibitor was 14 days (median) in our study. Therefore, we were able to assess the very early

metabolic response to therapy, which offers the chance of early treatment optimization.

Strategies other than metabolic imaging have been used to assess the early response to systemic therapy in breast cancer. Tahmassebi et al. [24] showed that diffusion-weighted magnetic resonance imaging (DWI-MRI) and machine learning techniques could predict a pathological response to neoadjuvant chemotherapy in breast cancer patients. However, FDG-PET seems to have superior accuracy compared to DWI-MRI in terms of axillary lymph node metastasis detection in primary breast cancer, which might indicate the superiority of metabolic imaging [25]. For pancreatic ductal adenocarcinoma, integrated PET-MRI could show that both PET and DWI MRI metrics are correlated with early response to chemotherapy [26]. Therefore, future studies should focus on the role of integrated PET-MRI imaging in early response assessment in breast cancer.

The present study had some limitations. The patient cohort was relatively small, which might prevent transferability to a large-scale cohort. However, repetition of FDG-PET/CT within days after the start of treatment is conducted very rarely. Thus, the present results warrant evaluation of the early metabolic response in larger cohorts – these trials might open the opportunity to test strategies of early treatment change in nonresponding patients. All patients enrolled into this pilot study had numerous distant metastases including liver lesions, which are known to be associated with a poor outcome [27]. Other negative prognostic markers like ESR-1 or p53 mutations were not known, as such analyses were not part of the regular clinical process [28]. Future studies should therefore integrate the early metabolic response with other known prognosticators of outcome for a comprehensive analysis.

Conclusion

Early metabolic changes assessed by FDG-PET after the initiation of CDK4/6 inhibitor therapy might identify patients at risk of treatment failure. Nonresponding patients might benefit from altered therapy regimes. Therefore, future studies evaluating early metabolic changes in larger cohorts seem warranted.

Statement of Ethics

This study was conducted as a retrospective analysis of patient data and it was approved by the Ethics Committee of the University of Duisburg-Essen (reference No. 20-9771-BO). Informed consent was not requested of the patients due to the nature of this study (anonymized patient data were evaluated by a researcher who was part of the treatment team). This research project complied with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors declare that they have no financial or nonfinancial competing interests. T.D. received advisory board honoraria from Novartis and Lilly. W.P.F. is a consultant for Endocyte and BTG and received fees from RadioMedix, Bayer, and Parexel outside of this work. A.W. has received advisory board honoraria from Roche, Novartis, Lilly, Pfizer, Eisai, Amgen, AstraZeneca, Pfizer, Daiichi Sankyo, Lilly, and Interplan, as well as a scientific grant from Novartis. No grants from any funding agency in the public, commercial, or not for profit sector were received for this research.

Author Contributions

T.D. and K.H.: conception and design. M.T., A.W., and T.D.: patient recruitment and sample and data collection. R.S., A.K., M.H., W.P.F., and K.H.: sample analysis. R.S. and A.K.: statistical analysis. R.S., A.K., M.T., A.W., M.H., W.P.F., K.H., and T.D.: data analysis and interpretation. R.S. and T.D.: drafting of this paper. All of the authors: critical revision and validation of the final version of this work.

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