Imaging Tumor Proliferation in Breast Cancer

Current Update on Predictive Imaging Biomarkers

Azadeh Elmi, MD, Elizabeth S. McDonald, MD, PhD, David Mankoff, MD, PhD*

KEYWORDS

• Breast cancer • PET imaging • Radiotracer • Tumor proliferation • Targeted therapies

KEY POINTS

- Imaging cell proliferation can provide an early measure of treatment response that can be used to guide personalized treatment.
- Imaging biomarkers of proliferation is especially beneficial in the setting of regimens exploiting cell cycle–targeted chemotherapies in combination with endocrine therapy.
- FLT uptake can quantify the S-phase fraction of cycling cancer cells.
- ISO-1 uptake can measure overall proliferative status of the tumor.

INTRODUCTION

Breast cancer is one of the most common cancers and the second leading cause of cancer-related death among women in the United States. Up to 6% of breast cancers are advanced or metastatic at the time of diagnosis, requiring chemotherapy.[1,2] Accelerated growth is a hallmark of cancer,[3] including breast cancer. The rapid expansion of treatments targeted to aberrant cell growth (eg, cell cycle–targeted chemotherapies for the treatment of metastatic breast cancer) allows for precise targeting of specific alterations in tumor cell proliferation pathway with the goal of reducing tumor cellular proliferation and increasing tumor cell death while minimizing toxicities associated with chemotherapy. The growing application of these targeted therapies motivates cell proliferation imaging techniques that can reflect the treatment response from cell cycle inhibition before morphologic and anatomic changes.

Evaluation of Ki-67 expression on biopsy samples is currently considered the gold standard for evaluating cell proliferation. A major drawback for clinical use of Ki-67 is that it requires serial biopsies of the primary tumor sites and/or metastatic lesions to assess changes in cell proliferation in response to therapy. Therefore, this technique is invasive and also prone to sampling errors and underestimation of tumor heterogeneity.[4,5] An

This work was supported in part by the Susan G. Komen Foundation (Dr E.S. McDonald CCR16376362 and Dr D. Mankoff SAC130060, Department of Energy Grant DE-SC0012476, and NIH Grant 5T32EB004311-13 for radiology research track residency). Dr E.S. McDonald is also the 2016–2018 American Roentgen Ray Society/Philips Healthcare Scholar. Grants support related research and support, in part, the effort of the coauthors.

Department of Radiology, Perelman School of Medicine, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA

* Corresponding author. Hospital of the University of Pennsylvania, 3400 Spruce Street, 1 Donner, Philadelphia, PA 19104.

E-mail address: david.mankoff@uphs.upenn.edu

PET Clin 13 (2018) 445–457
https://doi.org/10.1016/j.cpet.2018.02.007

imaging biomarker is an attractive noninvasive alternative that can provide spatial data of primary and metastatic disease. Imaging cell proliferation can provide an early noninvasive indicator of cancer therapeutic response that is used to guide personalized treatment with identifying patients that benefit from those that might not need or benefit from the therapy, early in the course of treatment to avoid toxicity and additional costs.

This review focuses on currently investigational cell proliferation imaging PET radiotracers to evaluate tumor proliferation in the setting of cell cycle–targeted chemotherapy and endocrine therapy for metastatic breast cancer. We review the underlying biology associated with cancer proliferation and cell cycle–targeted drugs, followed by a review of the mechanistic underpinnings of cell proliferation tracers, and finally, their application to therapy targeted to aberrant breast cancer proliferation.

CELL CYCLE AND PROLIFERATION CONTROL: ENHANCING ENDOCRINE THERAPY WITH CELL CYCLE–TARGETING AGENTS

Proliferating cells must progress through four phases of cell cycle (G1, S, G2, and M); however, they may exit the cell cycle and enter quiescence (G0) when stressed or deprived of biologic stimuli (eg, in breast cancer with estrogen deprivation).[6,7] Cyclin-dependent kinases (CDKs) play a key role in controlling cell cycle progression. Among these kinases, CDK4/6 is the key regulator of G1 to S transition by controlling transcription of genes necessary for cell cycle progression. This kinase is activated on binding to cyclin D, leading to expression of genes required for S-phase entry.[8] The tightly regulated cyclin D-CDK4/6 complex is frequently disrupted in breast cancer, with subsequent inactivation of the G1-S checkpoint, which can lead to aberrant growth and ultimately tumor formation.[8,9]

Another important player in breast cancer is estrogen pathway. Estrogen stimulates the proliferation of estrogen receptor (ER)-positive cancer cells via activation of cyclin D (**Fig. 1**).[10] Approximately 70% to 75% of breast cancers express hormone receptors and most of these cancers depend on estrogen signaling for their growth and survival.[11] Endocrine therapy has been the mainstay of treatment in patients with metastatic ER-positive disease and when compared with conventional chemotherapy, it is primarily cytostatic.[12] Endocrine therapy–induced growth inhibition traps cancer cells at the G0/G1 phase of the cell cycle.[13] Subsequently, the apoptotic pathway is activated for some of these cells resulting in cell death. However, fractions of the cells might remain in quiescence and evidence suggests that these cells may play an important role in recurrences of hormone-responsive breast cancer, reflecting underlying tumor dormancy.[14]

Tamoxifen is a selective ER modulator and is used to treat early and advanced ER-positive breast cancer. In breast tissue, tamoxifen is a selective ER down-regulator resulting in blockade of the estrogen-signaling pathway.[15] Prior studies demonstrated clear survival benefits in patients with ER-positive breast cancer. For example, the EBCTCG study reported approximately 30% reduction in breast cancer mortality for 15 years after diagnosis along with substantial reduction in cancer recurrence in patients reviving tamoxifen.[16] Fulvestrant is another ER modulator, approved for the treatment of ER-positive metastatic breast cancer after standard antiestrogen

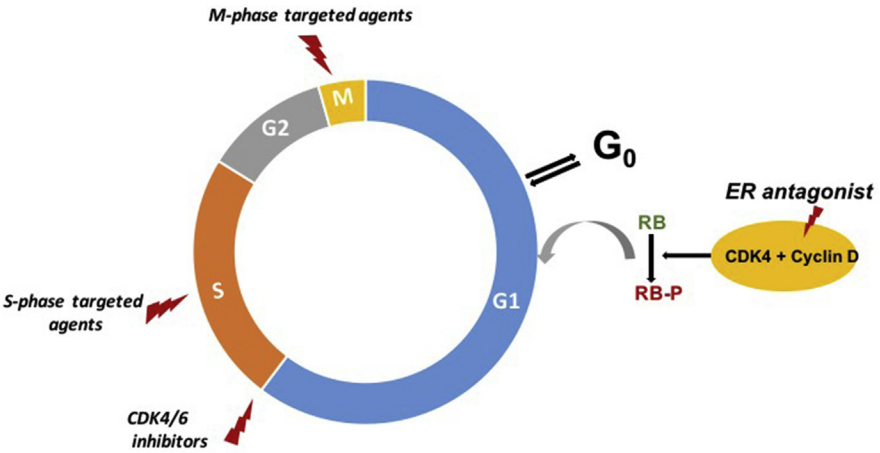

Fig. 1. Cell cycle–targeted chemotherapeutics and estrogen modulators.