mTOR Inhibitors in the Treatment of Breast Cancer

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Efforts to identify clinical biomarkers of response or resistance to mTOR inhibitors are ongoing. This review will summarize results of preclinical and clinical studies as well as ongoing clinical trials with mTOR or dual PI3K/mTOR inhibitors.

Introduction

The mTOR pathway

The phosphatidylinositol 3-kinase (PI3K)/Akt pathway, of which mammalian target of rapamycin (mTOR) protein is an important component, is commonly dysregulated in cancer. TOR protein, a highly conserved serine/threonine protein kinase, was first identified in 1991 through yeast studies examining the mechanism of rapamycin.[1] Complex regulatory mechanisms of the mTOR signaling pathway have been elucidated. These mechanisms have been important in the development of mTOR inhibitors for treatment of cancer and also in identifying predictors of response or resistance.

mTOR controls various cellular processes, including growth, survival, and autophagy. It receives input from upstream growth factor receptors, such as the PI3K pathway, and senses nutrient availability; its central role is in integrating these signals and altering cellular processes. Based on nutrient availability, the mTOR pathway can either promote cell growth or it can inhibit growth during the nutrient deprivation state.[2] Autophagy, a catabolic process involved in eradicating damaged cellular material, is under the delicate control of the mTOR pathway. It is utilized as an adaptive rescue mechanism for starving cells to conserve energy and is highly dependent on nutrient availability.[3]

The mTOR pathway also receives input from the adenosine monophosphate–activated protein kinase (AMPK) pathway. The AMPK pathway senses cellular energy and negatively regulates the mTOR pathway through the tuberin (TSC1)/hamartin (TSC2) complex. When energy stores are low, AMPK and TSC2 are activated, thereby inhibiting the mTOR pathway. An additional negative regulator of mTOR is phosphatase and tensin homolog (PTEN), which also tightly regulates the PI3K pathway.[4] There are two distinct complexes of mTOR—mTORC1 and mTORC2—which have independent regulatory mechanisms and exert their cellular growth effects through different downstream targets. Activated mTOR-raptor complex 1 (mTORC1) results in enhanced protein synthesis and also inhibits PI3K signaling. Activated mTOR-rictor complex 2 (mTORC2) promotes cell survival.[4]

PI3K/mTOR signaling in breast cancer

Activating PI3K mutations are frequent in human cancers and have been identified as oncogenic, making this pathway an attractive therapeutic target in cancer.[5] These mutations can occur in any component of the PI3K pathway, resulting in its dysregulation; a number of mechanisms, including mutations, methylation, and loss of heterozygosity, may be involved. PIK3CA (p110 catalytic subunit alpha) mutations have been identified as a common occurrence in breast cancer,[6] with a higher frequency in the estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-positive subtypes than in triple-negative breast cancer (TNBC).[7] Studies have confirmed that the PIK3CA gene is among the most highly mutated genes in breast cancer: mutations occur at a frequency of 27% to 36%.[8,9] One such study evaluated the mutational spectrum of PIK3CA by breast cancer subtype,[8] determined by gene expression profiling.[10,11] The PIK3CA somatic mutation spectrum differed both by the frequency of mutation and by the type of PIK3CA mutation seen in each subtype. The luminal A subtype of breast cancer had the highest frequency of PIK3CA mutation (45%), and the basal subtype had the lowest (9%). These data are consistent with the results of prior studies, as luminal A and basal-like subtypes roughly correspond to ER-positive and triple-negative breast cancer by immunohistochemistry (IHC), respectively. Even though PIK3CA
mutations are oncogenic, they are a good prognostic factor and are associated with improved survival.[12] This is important to consider when assessing patient survival in trials in patients with PIK3CA mutations. Additional PI3K pathway alterations in breast cancer include Akt and PTEN mutations, or loss of PTEN protein.[7,13] Activation of the PI3K pathway in breast cancer can occur via a PI3K pathway component aberration or through activation of another crosstalk pathway. Beyond identifying PI3K pathway mutations for understanding breast cancer biology, there are important considerations when this information is used for patient selection for treatment. The specific PI3K mutations and the altered components of the PI3K pathway may both impact treatment response.

**Development of mTOR inhibitors in cancer**

Rapamycin, a macrolide, was first isolated from a soil sample on Easter Island (Rapa Nui) in 1975, and was shown to have antifungal properties.[14] It was initially used clinically as an immune suppressant to prevent allograft rejection in renal transplant patients. Sirolimus (Rapamune), a rapamycin analog (rapalog), has been shown to inhibit the growth of cancer cell lines and xenografts from different tumor subtypes.[15,16] The first generation of mTOR inhibitors target mTORC1, but they do not bind to mTORC2, which is mostly considered to be rapamycin-insensitive.[2] However, there are limited data that rapamycin reduces mTORC2 levels and inhibits Akt activation.[17] Targeting only mTORC1 with rapalogs leads to increased signaling through upstream receptor tyrosine kinases and increased Akt activation, which promotes cell survival. It has been speculated that rapalogs have had limited clinical activity in cancer due to this mechanism, as well as activation of parallel signaling pathways. This limitation of rapalogs has fueled development of alternate methods of targeting the PI3K signaling pathway, with either adenosine triphosphate (ATP)-competitive mTOR inhibitors that target both mTORC1 and mTORC2, or by using dual PI3K/mTOR inhibitors. Several mTORC1 inhibitors are in clinical trials for various tumor subtypes, including everolimus (Afinitor), temsirolimus (Torisel), and ridaforolimus (AP23573). Temsirolimus was the first rapalog approved by the US Food and Drug Administration (FDA); it was approved in 2007 for the treatment of advanced renal cell cancer.

In breast cancer, the majority of studies have exploited the use of mTORC1 inhibitors in ER-positive or HER2-positive breast cancers, primarily to reverse treatment resistance. The focus of this review will be these preclinical and clinical studies by breast cancer subtype. We will also discuss ongoing breast cancer clinical studies using ATP-competitive mTOR inhibitors, which target mTORC1/mTORC2, and dual PI3K/mTOR inhibitors.

**Hormone Receptor-Positive Breast Cancer**

**Preclinical studies**

Preclinical studies, using hormone receptor (HR)-positive cell lines, have demonstrated activation of the PI3K/mTOR pathway after long-term estrogen deprivation.[18,19] Based on these studies, it appeared that estrogen-deprived cells relied heavily on the PI3K signaling pathway, making this an important mechanism of acquired endocrine resistance. This suggested that priming of the PI3K pathway with anti-hormonal treatment might be important in sensitizing these cells to PI3K/mTOR inhibitors. A natural next step was to use combination therapy, simultaneously targeting both the ER and PI3K pathways. Early combination studies showed that rapalogs were synergistic with anti-estrogens, including tamoxifen and letrozole (Femara); blocking both pathways not only enhanced antitumor activity but also reversed endocrine therapy resistance related to PI3K signaling.[20-22] Moreover, high Akt activity has also been shown to contribute to resistance to endocrine therapy,[23] and this also can be reversed by rapalogs.[20,22]

**Clinical studies**

**Metastatic setting.** Almost all patients with HR-positive breast cancer treated with endocrine therapy develop tumor resistance to treatment. Preclinical data, as described earlier, implicate the PI3K/mTOR pathway in acquired resistance to endocrine therapy, and synergistic preclinical anti-tumor activity has been seen with the combination of rapalogs and anti-estrogens. Based on this biological rationale, clinical trials have combined mTORC1 inhibitors and endocrine therapy in HR-positive breast cancer. Initial studies with temsirolimus and everolimus as single agents in the metastatic setting demonstrated response rates of 9% to 12%.[24,25] Another study with temsirolimus alone was limited to HR-positive or HER2-positive metastatic breast cancer, to enrich it...
Clinical activity was again limited. Primary tumors from this study were analyzed for PIK3CA mutations, but no association was seen with clinical response. A limitation of this study is that the PIK3CA mutation status of primary tumors was analyzed, as opposed to the metastatic site, which can be discordant.

The next approach was to combine anti-estrogens and mTORC1 inhibitors in clinical trials. A randomized phase II study of HR-positive metastatic breast cancer tested combination letrozole and temsirolimus vs letrozole alone and found that patients who received combination therapy had superior median progression-free survival (PFS) (13.2 vs 11.6 months). However, the clinical benefit rate (CBR) and the objective response rate (ORR) for patients in the combination arm were not significantly different from the rates in patients who received letrozole alone. Given these somewhat encouraging results, a large randomized phase III trial (N = 1112) was conducted in postmenopausal women with metastatic disease, with letrozole either alone or in combination with temsirolimus as first-line endocrine therapy. The trial was terminated early due to lack of benefit.

It has been speculated that this trial failed since it limited the use of mTOR inhibition in combination with endocrine therapy to the first-line metastatic setting. Given lack of prior hormonal therapy exposure, the tumors might not have been dependent on the PI3K/mTOR pathway, thereby remaining insensitive to mTOR pathway inhibition. This highlights the need for identification and selection of patients, whose tumors are dependent on PI3K pathway activation.

The Tamoxifen Plus Everolimus (TAMRAD) study (N = 111) randomized patients with prior exposure to an aromatase inhibitor (AI) in the metastatic setting, to tamoxifen alone versus combination tamoxifen and everolimus. This study demonstrated improvement in CBR (42% vs 61%; P = .045), the primary endpoint, and in time to progression (TTP) (4.5 vs 8.6 months; hazard ratio [HR] = 0.54; 95% confidence interval [CI], 0.36–0.81; P = .002) favoring the combination treatment. This supports that prior endocrine therapy resulting in priming of the PI3K/mTOR pathway may allow for meaningful synergy through attempts to overcome acquired endocrine resistance. In an exploratory analysis, patients were stratified based on primary hormone resistance, defined as relapse during adjuvant AI therapy or progression within 6 months of AI treatment in the metastatic setting, or secondary hormone resistance, defined as late relapse or progression on an AI in the metastatic setting more than 6 months after treatment. A higher CBR (48% vs 74% [secondary]; 36% vs 46% [primary]) and increased TTP (5.5 vs 14.8 months; HR = 0.46; 95% CI, 0.26–0.83; P = .009 [secondary]; 3.8 vs 5.4 months; HR = 0.70; 95% CI, 0.40–1.21; P = nonsignificant [primary]) was predominantly observed in patients with secondary hormone resistance in the everolimus arm.

A phase III trial, Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2), enrolled 724 patients with HR-positive advanced breast cancer to assess the efficacy of everolimus (at a dose of 10 mg per day) and exemestane (Aromasin), in patients with disease refractory to nonsteroidal AIs, including letrozole or anastrozole (Arimidex). An improved median PFS was observed by both local and central assessment with the combination of exemestane and everolimus (2.8 vs 6.9 months; HR = 0.43; 95% CI, 0.35–0.54; P < .001 [local]; 4.1 vs 10.6 months; HR = 0.36; 95% CI, 0.27–0.47; P < .001 [central]). Overall survival results have not been reported. A total of 23% of patients receiving everolimus had serious adverse events compared with 12% receiving placebo, resulting in everolimus discontinuation in 19% of the combination group vs 4% in the placebo group. The most common grade 3 or 4 events with combination therapy were stomatitis, anemia, hyperglycemia, dyspnea, fatigue, and pneumonitis. Notably, there were seven deaths attributed to adverse events (1%) in the everolimus arm; these were due to sepsis, pneumonia, tumor hemorrhage, cerebrovascular incident, renal failure, and suicide.
with other anti-hormonal therapies and even chemotherapies, in various lines of metastatic disease (Table).

In summary, trials of combination endocrine therapy and mTORC1 inhibitors in metastatic HR-positive breast cancer have demonstrated variable results. Single-agent temsirolimus or everolimus has limited clinical activity in metastatic breast cancer. A large study that combined temsirolimus with letrozole vs letrozole alone in first-line hormonal therapy for metastatic disease found no benefit from the combination. Two trials have found that combination everolimus and tamoxifen (TAMRAD study) or combination everolimus and exemestane (BOLERO-2) is more effective than either endocrine agent alone. The variability among the reported studies may be related to patient selection, prior endocrine therapy exposure, and the specific drug combination being tested. It is noteworthy that both of the positive studies selected patients who were previously exposed to endocrine therapy in the metastatic setting. Thus, prior endocrine therapy exposure may be an important factor in priming the PI3K/mTOR pathway and thereby sensitizing the tumors to inhibition of this pathway.

**Adjuvant/neoadjuvant setting.** Everolimus was studied as a single agent in a neoadjuvant trial and was associated with a significant reduction in Ki67 after 14 days of therapy.[32] A neoadjuvant, randomized study in postmenopausal women (N = 270) with ER-positive breast cancer compared letrozole and everolimus vs letrozole and placebo.[33] There was an improved clinical response rate and decreased proliferation in the everolimus-plus-letrozole arm compared with letrozole alone. Response was seen in both wild-type and mutant PI3K tumors. In addition, a reduction in phospho-S6, a pharmacodynamic marker, was noted in post-treatment biopsies in the everolimus-containing arm, signifying that mTOR was being inhibited at the dose used.[33]

In the adjuvant setting, a phase III randomized trial is evaluating the role of combining everolimus with standard adjuvant endocrine therapy, for women with high-risk breast cancer (Table). Based upon the available data, there is no standard role for adjuvant or neoadjuvant use of mTOR or dual PI3K/mTOR inhibitors in combination with endocrine therapy or chemotherapy.

### HER2-Positive Breast Cancer

**Preclinical studies**

A link between Akt/mTOR pathway activation and HER2 overexpression was first established in primary breast tumors, implicating the pathway in progression of HER2-positive breast cancer.[34] Trastuzumab resistance is caused by hyperactivation of the PI3K pathway, resulting from either PIK3CA mutation, loss of PTEN, or activation of parallel pathways.[35,36] Treatment with mTOR inhibitors is an effective strategy for overcoming preclinical trastuzumab resistance[37] secondary to PTEN loss.[38] Unlike trastuzumab, lapatinib (Tykerb) sensitivity is independent of PI3K pathway activation.[39] A study aimed to identify pathway alterations that play a role in lapatinib resistance. Similar to prior studies that have assessed mechanisms of lapatinib sensitivity, the PI3K signaling pathway was not found to be hyperactivated in the lapatinib-resistant cells. However, the resistant cells demonstrated activation of mTORC1 by an Akt signaling–independent mechanism. This was evidenced by downstream activation of mTOR effectors; moreover, these lapatinib-resistant cells were sensitive to mTOR inhibition using a rapalog and a dual PI3K/mTOR inhibitor.[40]

**Clinical studies**

**Metastatic setting.** There is a biological rationale for the use of PI3K/mTOR pathway inhibitors, in both trastuzumab- and lapatinib-refractory disease, based on preclinical data. A dose-escalation study of everolimus in combination with paclitaxel and trastuzumab in trastuzumab-refractory HER2-positive metastatic breast cancer has been reported.[41] This study demonstrated clinical activity with an ORR of 44%, and control of disease for 6 months or more in 74% of the patients. Based on this study, paclitaxel and trastuzumab with either everolimus at a dose of 10 mg per day or placebo is being tested in a phase III randomized study (Table). An additional phase I study combined everolimus with weekly trastuzumab and vinorelbine in pretreated HER2-positive metastatic breast cancer.[42] Everolimus doses of 5 mg per day and 30 mg per week were established as safe for further development, with grade 3 or 4 neutropenia as dose-limiting. Significant anti-tumor activity was noted, with an ORR of 19.1%, disease control rate of 83%, and median PFS of 30.7 weeks. This regimen is now being tested for the treatment of progressive or new brain metastases in patients with HER2-positive breast cancer. Everolimus crosses the blood-brain barrier, and patients who progress after radiation are eligible for treatment on this study (Table).
Early clinical studies have also combined dual PI3K/mTOR inhibitors with trastuzumab. A phase I/ib dose-escalation study of BEZ235, a dual PI3K/mTOR inhibitor, with trastuzumab aimed to enrich for patients with PI3K pathway alterations by limiting the study to patients with mutations in PIK3CA or PTEN or loss of PTEN by IHC in tumor samples. The maximum tolerated dose (MTD) for BEZ235 is estimated to be 600 mg per day in combination with trastuzumab, and this dose is being carried forward to the dose-expansion cohort. The combination also appears to be clinically active, with a CBR of 27%. In this study, there does not appear to be an association between PI3K pathway alteration and response.[43] Given the short half-life of BEZ235, a twice-daily schedule is under investigation in a phase Ib/II study in combination with trastuzumab (Table). Studies with other combinations, including temsirolimus and neratinib (HKI272) (phase I/II) or everolimus and lapatinib (phase II) are ongoing (Table).

**Adjuvant/neoadjuvant setting.** A randomized, phase II study in HER2-positive early-stage breast cancer is assessing whether adding everolimus to trastuzumab in the neoadjuvant setting improves clinical tumor response rate (Table).

### Triple-Negative Breast Cancer Preclinical studies

There is strong evidence that the PI3K pathway is commonly altered in TNBC. Copy number, gene expression, proteomic, and sequencing studies in TNBC have shown the following pathway alterations: (a) a loss of PTEN, which is a negative regulator of the PI3K pathway, in up to a third of TNBCs[44]; (b) PIK3CA and PTEN mutations[45]; and (c) activation of Akt with PTEN loss.[46] A recent study compared TNBC to HER2-positive or ER-positive breast cancer and found a relatively low (9%) PIK3CA mutation frequency. However, using a pathway-based approach, this study highlighted that despite the low frequency of PIK3CA mutations, inferred PI3K activity was the highest in basal-like breast cancers.[8] This increased pathway activity may be due to alternative mechanisms, such as PTEN loss; moreover, this finding provides strong support for using PI3K/mTOR inhibitors in this subtype. The basal-like subtype of TNBC has been shown to be sensitive to mTORC1 inhibitors, in both in vitro and in vivo studies, resulting in cell growth inhibition.[46,47] TNBC behaves as a clinically heterogeneous disease, and this heterogeneity was well-characterized using gene expression profiling of primary TNBC tumors.[48] Clustering analysis of TNBC gene expression data identified six subtypes, and tumors within the mesenchymal and mesenchymal stem cell-like subtypes were sensitive to dual PI3K/mTOR inhibitors.[48] The frequent alterations in the PI3K pathway in TNBC and preclinical data with PI3K/mTOR inhibitors provide a strong rationale for further investigation of PI3K/mTOR inhibitors in TNBC.

**Clinical studies**

**Metastatic setting.** There are very limited clinical data on TNBC treated with either rapalogs or PI3K/mTOR inhibitors. A phase II trial with everolimus and carboplatin in patients with metastatic TNBC found a CBR of 38% (8 of 21 assessable patients) in a pretreated population.[49] A phase I study in metastatic TNBC, using a combination of temsirolimus, cisplatin, and erlotinib (Tarceva), is ongoing (Table).

**Adjuvant/neoadjuvant setting.** A randomized phase II neoadjuvant study in TNBC compared paclitaxel with or without everolimus followed by FEC (T-FEC). Everolimus was administered at a dose of 30 mg orally weekly for a total 12 weeks, concurrently with paclitaxel. There was no significant difference with the addition of everolimus in the pathologic complete response rate (pCR; 26% vs 30% for everolimus arm) or 12-week response rate by ultrasound (30% vs 48% for everolimus arm).[50] The clinical activity of everolimus in combination with cisplatin and paclitaxel is being evaluated in a randomized phase II neoadjuvant study in TNBC disease (Table).

### PI3K Pathway Inhibitors and Drug Combinations in Clinical Trials
Inhibitors of the PI3K/ mTOR Pathway

The PI3K pathway is very tightly regulated, and there is crosstalk between it and several other pathways.[51] In complex pathways with negative regulatory feedback loops and other escape pathways, such as the PI3K pathway, blockade of one component of the pathway is unlikely to accomplish complete inhibition of the pathway. It has been speculated that this is one of the reasons for poor clinical responses with allosteric mTORC1 inhibitors or rapalogs alone that are effective against mTORC1 but not mTORC2. This has propelled the development of novel ATP-competitive inhibitors of mTOR kinase activity, which block both mTORC1 and mTORC2, as well as the development of dual PI3K/mTOR inhibitors. A number of dual mTORC1/2 inhibitors have been identified, including INK128 (Intellikine), CC223 (Celgene), OSI-027 (OSI Pharmaceuticals), AZD8055 (AstraZeneca), AZD2014 (AstraZeneca), and Palomid 529 (Paloma Pharmaceuticals) (Figure). Dual PI3K/mTOR inhibitors (Figure) have also been developed in the hope of overcoming the loss of feedback inhibition or PI3K activation observed with rapalogs. The mTORC1 pathway is one of the prominent negative feedback regulators of the PI3K pathway; inhibition of mTORC1 can release this feedback inhibition and activate the PI3K pathway. BEZ235, a dual PI3K/mTOR inhibitor, showed higher anti-proliferative activity than rapamycins in a preclinical study with multiple cancer cell lines, and it had antitumor activity in a trastuzumab-resistant breast cancer cell line.[52] In breast cancer, dual PI3K/mTOR inhibitors are being combined with everolimus, endocrine therapies (exemestane and letrozole), chemotherapy (paclitaxel), and anti-HER2 therapy (trastuzumab) (Table). Combinations of MEK and PI3K pathways inhibitors are being explored in attempts to block escape pathways, which may become prominent when the PI3K pathway is inhibited. There is also a rationale for combining insulin-like growth factor-1 receptor (IGF1R) signaling inhibitors with mTOR inhibitors, since IGF1R is hyperactivated as a result of the negative feedback loop release that occurs with mTORC1 inhibition.[53]

Predictors of Response or Resistance

The identification of markers that predict for response to PI3K/mTOR inhibitors can significantly aid in selection of patients who are most likely to benefit from this targeted therapy. Preclinical data indicate that cell lines with \textit{PIK3CA} or \textit{PTEN} mutations, as well as elevated basal and post-treatment phospho-Akt levels, are likely to be sensitive to rapamycin. Based on this, there is a need to assess phospho-Akt as a potential biomarker for rapamycin response.[54] Several clinical studies have evaluated \textit{PIK3CA} and \textit{PTEN} mutation status in tumors and have not conclusively shown that PI3K pathway mutations sensitize tumors to PI3K/mTOR inhibitors. \textit{PIK3CA} mutations were analyzed in tumors including breast, cervical, endometrial, and ovarian, from a single-institution phase I program.[55] Of a total of 140 patients, \textit{PIK3CA} mutations were identified in 25 (18%) of these patients. A higher response rate was seen in patients with \textit{PIK3CA} mutations, but six of the seven patients who experienced tumor response had received a combination of a rapalog and a cytotoxic drug (liposomal doxorubicin). It is difficult to draw any conclusions from this study regarding an association between therapy response to PI3K/mTOR inhibitors with \textit{PIK3CA} mutation status, since the study was small and only included patients being treated with rapalogs.[55] The majority of the clinical trials in the metastatic setting evaluate the primary tumors for PI3K pathway mutations; studies have shown that there may be discordance between the \textit{PIK3CA} mutation status of the primary tumor and that of the metastatic site, likely due to tumor evolution.[27] It is possible that an association between therapy response to PI3K/mTOR inhibitors and mutation status has been missed because the mutation analysis does not capture the current state of the tumor. In addition, most clinical trials have assessed only a small number of mutations in the PI3K pathway. Analysis of mutations has mostly been limited to \textit{PIK3CA} or \textit{PTEN} genes.
highly complex nature of the PI3K pathway, we are likely not capturing the entire spectrum of mutations in this pathway.

**Toxicity and Management**

The most frequent adverse events seen with mTOR inhibitors include stomatitis, rash, asthenia, hyperlipidemia, thrombocytopenia, fatigue, anorexia, hyperglycemia, elevated transaminases, pruritus, and anemia. We will discuss screening and management of common metabolic side effects, including hyperlipidemia and hyperglycemia, as well as noninfectious pneumonitis.

**Metabolic effects**

The incidence rates of metabolic effects with either mTORC1 or dual mTORC1/mTORC2 inhibitors have a wide range; hyperglycemia is seen in 22% to 50%, hypertriglyceridemia in 27% to 71%, and hypercholesterolemia in 24% to 76%.[56] High-grade adverse events are rare for all metabolic effects. The PI3K-Akt-mTOR (PAM) Task Force of the National Cancer Institute recently convened to establish guidelines for managing hyperlipidemia and hyperglycemia in cancer patients.[56] They also discussed insights into the mechanisms associated with this phenomenon, which is predominantly related to promotion of insulin resistance by PAM pathway inhibition. Overall, these metabolic effects may be more prominent in patients with insulin resistance or who are at higher risk because of family history. Typically, with mTOR inhibitors, elevations in total cholesterol, lactate dehydrogenase (LDL), and triglyceride levels are primarily seen. The Task Force recommends obtaining a complete fasting lipid panel at baseline and then at least at every cycle for phase II and later-phase studies; for phase I studies, more intense monitoring, once per week for the first two cycles, is recommended. Thresholds for intervention with drug therapy vary depending on a patient’s estimated life expectancy. In general, the goals should be to keep fasting triglycerides < 300 mg/dL and LDL < 190 mg/dL, for patients without any cardiac risk factors. If the patient’s life expectancy is estimated to be less than 1 year, then drug therapy to lower triglycerides is needed for levels > 500 mg/dL, primarily to prevent complications of hypertriglyceridemia, such as pancreatitis. For hyperglycemia screening for patients on PAM pathway inhibitors, a random glucose test is recommended at every visit for non-diabetics, and at least once per day of the first cycle for high-risk patients.[56] If hyperglycemia is sustained or of high grade even in asymptomatic patients, treatment with metformin as first-line therapy is recommended.

Incorporation of these guidelines is important for all ongoing clinical studies but may have an even higher impact in clinical trials in which therapies are being used to treat early-stage patients, with curative intent. The long-term consequences of uncontrolled hyperglycemia and hyperlipidemia may be more severe in these patients, and therefore they are likely to benefit the most from intense screening and treatment.

**Noninfectious pneumonitis**

A known class effect of mTOR inhibitors is noninfectious pneumonitis, and it is of unclear etiology. Clinical data on pneumonitis were recently summarized from an advanced renal cell cancer study of 416 patients, in which 274 patients were randomized to receive everolimus.[57] Clinical presentation of mTOR inhibitor–associated pneumonitis was typically with a cough or dyspnea or both. The pattern on radiologic imaging varied from ground-glass infiltrates to more diffuse infiltrates. Pneumonitis occurred in patients from 3.4 to 36.7 weeks (median of 15.4 weeks) following the start of therapy. For monitoring for pneumonitis, routine chest X-rays and CT scans were obtained every 8 weeks, and pulmonary function tests (PFTs) were performed at baseline. Among 13.5% of patients suspected to have clinical pneumonitis, 3.3% of cases were grade 1 (mostly asymptomatic), 6.6% were grade 2 (not interfering with daily living), and 3.6% were grade 3 (interfering with daily living or oxygen indicated), but there was no grade 4 (life-threatening) pneumonitis. Pneumonitis appeared to be increased in patients with baseline radiographic abnormalities. Of the patients who had grade 3 toxicity, 2 out of 10 patients eventually died of pulmonary complications related to infection and progression of disease. However, others had a good outcome when managed using guidelines as outlined in the study. Based on these data, the authors made recommendations for the treatment of pneumonitis during everolimus therapy; these included the use of steroids, dose adjustment, or treatment discontinuation. Everolimus should be held for grade 2 and 3 toxicity, and may be re-initiated at a lower dose after steroid treatment and resolution of clinical symptoms. If grade 4 toxicity occurs, everolimus should be discontinued permanently.[57] Among five breast cancer studies with everolimus, the adverse event of noninfectious pneumonitis
was analyzed.[58] In the majority of the subjects, pneumonitis was diagnosed and monitored by CT imaging and PFTs. The highest pneumonitis grade was 3, and its incidence ranged between 2.2% and 6%; in all cases, it resolved with appropriate management. A recent meta-analysis of 2233 patients assessed pulmonary toxicity with everolimus and temsirolimus in published trials of patients that included 989 breast cancer patients. The incidence of all pulmonary toxicity was 10.4% among patients taking mTOR inhibitors, and 2.4% had high-grade toxicity.[59]

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN) guidelines include the option of incorporating everolimus into endocrine therapy for patients with advanced HR-positive breast cancer who have progressed on at least one prior nonsteroidal AI in the metastatic setting. Currently, we have data on improvement in PFS but not overall survival with this regimen. Thus, while the addition of everolimus to exemestane appears to prolong PFS, the combination is substantially more toxic than exemestane alone. Without evidence of clear improvement in overall survival, the clinician and patient must balance the potential for improvement in anti-tumor activity with the increased risk of toxicity and corresponding reduction in overall quality of life. The decision-making is further complicated by the relatively high monthly cost of everolimus, which is estimated to be $7,000 to 8,000 per month for the drug only, not including the additional expense of everolimus toxicity monitoring or treatment.

Conclusion

In the investigation of breast cancer, the development of mTOR pathway inhibitors has evolved from single-agent rapalogs to dual mTORC1/mTORC2 inhibitors and dual PI3K/mTOR inhibitors. In advanced HR-positive breast cancer, there is now a potential role for the combination of everolimus with a steroidal AI in patients previously exposed to a nonsteroidal AI. It is reasonable to consider the use of this treatment strategy for patients with endocrine therapy–resistant breast cancer, as supported by the NCCN guidelines. The improvement in PFS however, is associated with increases in toxicity and expense, without a known impact on overall survival. There are no data currently supporting the combination of mTOR inhibitors with endocrine therapy in first-line treatment of metastatic breast cancer or in the adjuvant setting. For our patients with metastatic breast cancer, quality of life is an important consideration when choosing therapies. The adverse effects of PI3K/mTOR pathway inhibitors do need to be taken into account when considering these agents, especially in patients with heavily pretreated metastatic disease. In patients with HER2-positive disease, the early clinical data on combinations of PI3K/mTOR inhibitors with anti-HER2 therapies are encouraging; however, the results from larger studies are not available yet. Unfortunately, no robust biomarkers to predict response or resistance to PI3K/mTOR pathway inhibitors have yet been identified to facilitate patient selection. Various combinations of dual PI3K/mTOR inhibitors and other pathway inhibitors, such as MEK or IGF1R, are being studied in clinical trials to either overcome loss of feedback inhibition or PI3K activation, as observed with rapalogs, or to block escape pathways, which may become prominent when the PI3K pathway is inhibited. The efficacy and safety of these combinations still need to be determined.

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