



Renal insufficiency in breast cancer patients; a review study

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ABSTRACT

The latest statistics and estimations indicated that breast cancer occurs in one-fourth of women worldwide and is responsible for one in six cancer deaths among women. A bilateral relationship seems to exist between breast cancer pathophysiology and kidney failure. Consideration should be given to this relationship when selecting a treatment protocol. This paper reviews the association between these two factors in breast cancer patients. There are many aspects to consider in the association between breast cancer and renal insufficiency. A breast cancer patient with normal kidney function is at risk of developing kidney failure due to paraneoplastic syndromes, hypercalcemia, and in rare cases, tumor lysis syndrome (TLS). In defining the optimal treatment protocol for each breast cancer patient, clinicians should consider the patient's basal glomerular filtration rate (GFR). Frequent renal clearance monitoring and taking immediate action at the time GFR begins to decrease will lower the rate of kidney failure in breast cancer patients. Lastly, patients with chronic kidney disease who are recently diagnosed with breast cancer may have higher morbidity and mortality compared to breast cancer patients with normal GFR. Further investigation is needed to lower morbidity and mortality in such patients.

Implication for health policy/practice/research/medical education:

A bilateral relationship seems to exist between breast cancer pathophysiology and kidney failure. Consideration should be given to this relationship when selecting a treatment protocol. To reach to optimal treatment protocol in breast cancer patients, clinicians should consider the patient's basal glomerular filtration rate (GFR). In addition, patients with chronic kidney disease who are recently diagnosed with breast cancer may have higher morbidity and mortality compared to breast cancer patients with normal GFRs. Further investigation is needed to lower morbidity and mortality in such patients. .

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Introduction

Based on the latest statistics and estimations, GLOBOCAN 2020, breast cancer occurs in one-fourth of women, making it the most common cancer in women worldwide. Breast cancer is responsible for one in six cancer deaths (15.5%) among women (1). Breast cancer mortality dramatically decreased from more than 60% in 1985 to 15.5% after different treatment methods were recommended for patients. These methods include chemotherapy, hormonal therapy, radiotherapy, and surgery (2,3). Today, the most appropriate treatment protocol is chosen based on cancer pathology, anatomical staging, and patient preferences (4). Despite improving patients' longevity and quality

of life, the side effects of cancer treatment are becoming a growing concern. Chemotherapy's side effects range from nausea/vomiting, fatigue, and alopecia to more severe conditions such as myelosuppression, leukemia, cardiotoxicity, thromboembolism, and ovarian failure (5). Good kidney function is necessary to metabolize and eliminate many chemotherapeutic agents (6). Renal insufficiency is a common complication in solid tumor patients. It is estimated that 50-60% of patients suffering from solid tumor cancers have below-normal glomerular filtration rate (GFR) (creatinine clearance mostly ranged between 60-90 mL/min) (7). Radiotherapy is another available treatment for breast cancer that can cause

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lymphedema, gastrointestinal symptoms, cardiotoxicity, and nephritis (8,9). To achieve the best results in breast cancer treatment, we should be aware of these side effects, prevent them if possible, or manage them early.

Several studies claim that impaired renal function is associated with greater cancer risk. This may be the result of a higher life expectancy in older patients. However, in younger patients with renal failure, the incidence of malignancies is still higher than that in the normal population. One of the possible reasons is an increased inflammatory response that can lead to tumorigenesis (10,11).

A bilateral relationship seems to exist between breast cancer pathophysiology and kidney failure. Consideration should be given to this relationship when selecting a treatment protocol. This paper reviews the association between these two factors in breast cancer patients. The following three categories describe breast cancer's relationship to renal failure:

1. Renal insufficiency due to breast cancer (paraneoplastic syndrome)
2. Renal insufficiency secondary to breast cancer treatment
3. Breast cancer in patients with reduced renal function

Renal insufficiency due to breast cancer

Breast cancer may affect renal function in several ways. These mechanisms are strongly associated with paraneoplastic syndrome. In paraneoplastic syndromes, renal dysfunction may be caused by ectopic hormone secretion, fluid and electrolyte imbalance, and antigen-antibody complex deposition in tubular and glomerular structures (12).

Paraneoplastic hypercalcemia

One of the most common paraneoplastic syndromes in patients with breast cancer is hypercalcemia. Approximately 80% of the time, hypercalcemia caused by malignant tumors occurs as a result of humoral factors produced by tumor cells (humoral hypercalcemia of malignancy [HHM]). Parathyroid hormone-related protein (PTH-rP) is the most common factor for increased calcium levels. Cancer cell RANK-L signaling induces PTH-rP secretion to enhance osteoclast activity. Among other factors, 1,25 dihydroxy vitamin D and parathyroid hormone (PTH) can contribute to hypercalcemia in breast cancer patients. The remaining 20% of patients with hypercalcemia secondary to breast cancer have osteolytic bone metastasis, which causes calcium release from the bone structure. It should be noted that sometimes the primary reason for hypercalcemia does not depend on breast cancer (e.g., primary hyperparathyroidism) (13).

Renal function (estimated by GFR) is associated with serum calcium levels in a bidirectional manner. Studies show a significant decrease in renal function as serum calcium levels increase. The underlying mechanisms of renal

failure secondary to hypercalcemia are nephrolithiasis, nephrocalcinosis, and chronic kidney disease (CKD). The severity of kidney disease is believed to be proportional to serum calcium levels. During CKD development, the kidneys' ability to excrete excessive amounts of calcium in the urine declines. Hypercalcemia is propagated later by secondary and tertiary hyperparathyroidism. CKD progression induced by hypercalcemia of malignancy produces a vicious cycle in which decreased renal function exacerbates hypercalcemia of malignancy (14).

To manage a patient with renal dysfunction following hypercalcemia of malignancy, patients should refrain from consuming calcium and hypercalcemic medications while maintaining hydration by infusing normal saline solution. By inhibiting bone resorption, bisphosphonates can reduce mineral loss. Another useful medication is corticosteroids, which are generally prescribed in hypercalcemia due to excessive 1,25 dihydroxy vitamin D (15).

Paraneoplastic glomerulonephritis

Although rare, glomerulonephritis (GN) can be either a primary presentation or a complication secondary to cancer. Generally, paraneoplastic GNs present with nephrotic syndromes, and membranous nephropathy is the most common form of GN resulting from solid tumors. Although paraneoplastic GN is less likely to accompany breast cancer as GI and lung tumors, some reports indicate that such complications may occur. Other than MN, there were cases of minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN), rapid progressive glomerulonephritis (RPGN), and focal segmental glomerulosclerosis (FSGS) in association with breast cancer. IgA nephropathy and thrombotic microangiopathy (TMA) have also been reported. Patients with unexplained growth of GN should be screened for undiagnosed malignancies, including breast cancer, particularly if they are older (over 60 years of age), smokers, or experience refractory growth of GN. In most cases, treatment of the underlying malignancy with or without immunosuppressants results in the complete remission of paraneoplastic GN. Relapse of GN after a period of remission in a person with cured malignancy suggests cancer relapse (12,16-18).

Tumor lysis syndrome

Tumor lysis syndrome (TLS) is a condition in which malignant cell lysis leads to a sudden rise in serum potassium, phosphate, and uric acid. In the absence of prompt management, this imbalance in serum composition can lead to acute kidney injury and permanent renal failure. In general, TLS is considered a complication of lymphoma and leukemia. Although rare, solid cancers, including breast cancer, can also cause TLS. To prevent this condition, serum uric acid, phosphate, and potassium should be monitored, and an adequate urine

output volume should be maintained. Several factors may contribute to TLS, including massive tumors, rapid response to chemotherapy, metastatic disease, preexisting azotemia, hyperuricemia, and high LDH levels. Preventing and treating TLS requires adequate hydration. Within proper hydration, loop diuretics can decrease potassium secretion and urine output. Urine alkalization is no longer suggested as it can cause renal injury itself. In the management of TLS, uric acid-lowering drugs such as allopurinol or rasburicase are essential (19-21).

Renal insufficiency as a side effect of breast cancer treatment

Endocrine therapy

Endocrine therapy has played an important role in preventing and treating breast cancer. GnRH agonists, aromatase inhibitors, and selective estrogen-receptor modulators (SERMs) are the main drug categories in the endocrine therapy of breast cancer (22).

In the meta-analyses by Lambertini et al, no renal side effects were reported for GnRH agonists (23). However, a potential side effect that should be considered, especially in young women with a desire to preserve their reproductive ability, is ovarian hyperstimulation syndrome (OHSS). The oocyte retrieval process using HCG or GnRH agonists is a procedure that can result in OHSS (24). OHSS can cause a large volume of third-space fluid retention and intravascular volume depletion, intraabdominal hypertension and compartment syndrome, and obstructive uropathy. Each of these conditions may lead to acute renal injury (25).

Aromatase inhibitors such as anastrozole and letrozole are another class of agents in hormonal therapy. Case reports show that these drugs can cause renal side effects. For example, however rare, anastrozole has been associated with GN. The type of GN in these patients was sclerosing and crescentic GN. Oral corticosteroids may be beneficial to revive kidney function (26,27). Henoch-Schoenlein purpura is another rare side effect of anastrozole. Discontinuation of anastrozole without any other treatment causes HSP to regress in two weeks (28). Aromatase inhibitors may induce and/or exacerbate hypercalcemia, making patients vulnerable to renal injury. (29-31) A new experiment on female rats showed that aromatase inhibitors, particularly anastrozole, are related to increased renal tubular injury features (32).

Tamoxifen and raloxifene belong to the class of SERMs and are essential medications for breast cancer treatment and prevent breast cancer in high-risk populations (33). Patients suffering from renal insufficiency usually tolerate SERMs without dose adjustment (34). Additionally, SERMs can lower phosphate and calcium levels and may correct hypercalcemia of malignancy or hypercalcemia due to treatment protocols, therefore the kidneys are protected against high serum calcium concentrations (35, 36). Some pieces of evidence suggest reno-protective

effects for SERMs and even anti-fibrotic effects that may be beneficial in patients under breast cancer treatment; the exact effect needs more investigation to become clear (37-39).

Chemotherapeutic agents

Alkylating agents

Platinum agents: Cisplatin and carboplatin, are effective in triple-negative breast cancer treatment (40). These agents can cause a significant decline in GFR and decrease serum magnesium and potassium levels due to renal tubular and vascular injury, which may lead to acute and/or chronic kidney insufficiency. Sufficient hydration combined with reno-protective agents reduces the risk of kidney injury (41).

Cyclophosphamide: Cyclophosphamide is commonly used to treat metastatic or recurrent breast cancer (42). Cyclophosphamide metabolites may cause glomerular nephritis, cortical tubular vacuolization, and interstitial edema. Bladder inflammation and hemorrhagic cystitis are other side effects that complicate the diagnosis and treatment of renal injury. It is recommended to add an antioxidant or renoprotective agent to the therapeutic regimen when using cyclophosphamide (43,44).

Anthracyclines

Doxorubicin, epirubicin, and other anthracyclines are widely used in adjuvant chemotherapy for breast cancer (45). Anthracyclines may cause glomerular and tubular injury and a sudden rise in serum urea and creatinine due to oxidative stress (46,47). Beta-blockers such as carvedilol and nebivolol, melatonin, ACE inhibitors, ARBs, and antioxidants are possible reno-protectives to use along with anthracyclines (48,49).

Antimetabolites

Pyrimidine analogs: Capecitabine and gemcitabine are used in metastatic breast cancer treatment. Capecitabine and its metabolites are generally eliminated in the urine (95%). It is usually well tolerated without serious renal side effects in patients with normal kidney function or slightly reduced renal function. A dose adjustment of capecitabine is necessary in patients with higher stages of renal dysfunction. Although rare, there are reports of capecitabine-induced nephrotoxicity; the condition is completely reversible with drug discontinuation (7,50,51). Gemcitabine-induced renal insufficiency has been reported more commonly. Hypertension, thrombocytopenia, and microangiopathic hemolytic anemia are all associated with gemcitabine nephrotoxicity. The onset or exacerbation of hypertension, anemia, or thrombocytopenia in a patient who received gemcitabine should raise suspicions of thrombotic microangiopathies. The prognosis is always favorable. Early discontinuation of gemcitabine is the key to at least partially regaining renal function (52-54).

Methotrexate

Methotrexate (MTX) is a dihydrofolate reductase inhibitor that is sometimes used in combination with other chemotherapeutic agents or after surgery/radiation therapy to treat breast cancer (55). MTX and its metabolites may cause renal tubular injury. The intensity of injury is proportionate to the plasma concentration and infusion rate of MTX. Predisposing factors for MTX-induced renal injury are male gender, low serum albumin levels, and administration of medications that interact with MTX elimination, such as furosemide. Since 90% of MTX and its metabolites are eliminated in the urine, MTX-induced kidney injury reduces the rate of MTX elimination, which in turn increases MTX side effects. Urine alkalization, proper hydration, and a lower drug infusion rate dramatically decrease MTX-induced renal injuries (56,57).

Vinca alkaloids

Vinorelbine is a semisynthetic vinca alkaloid that inhibits tubulin polymerization and cell mitosis. It is an effective agent for many breast cancer patients as first-line therapy or treatment of metastatic/recurrent breast cancer (58,59). Vincristine is another medication that is effective in the advanced stages of breast cancer (60). Generally, Vinorelbine and Vincristine are likely to cause inappropriate antidiuretic hormone (SIADH) secretion by affecting neurohypophysis. SIADH may appear 1-2 weeks after receiving vinca alkaloids (61). Hemolytic uremic syndrome has been casually reported as a consequence of vincristine usage (62). In a few trials, grade 1/2 nephrotoxicity was seen in approximately 22% of patients receiving a combination of cisplatin/vinorelbine. It is not obvious whether cisplatin, vinorelbine, or both are responsible for such complications (63,64).

Antimicrobial agents

Taxanes, such as docetaxel and paclitaxel, are widely used either alone or in combination with other agents in advanced metastatic cancer. These are also useful in adjuvant and neoadjuvant therapies (65). Although there is not enough available literature on paclitaxel nephrotoxicity, some papers recommend being cautious about the potential harm it may cause to the kidneys (66). Docetaxel is another taxane that is metabolized in the liver by cytochrome P450. Its metabolites are usually found in bile and eliminated in feces. Docetaxel's pharmacokinetics have a kidney-independent nature that makes it a safe choice even for patients with renal insufficiency. There is no need to adjust the dose of docetaxel in patients with a reduced GFR. Unexpected acute tubular damage has been reported in a few cases following docetaxel use. The mechanism for developing these injuries is yet to be understood (67,68). One possible explanation is oxidative stress and apoptosis induction in kidney cells following docetaxel use. Selenium can reduce docetaxel

nephrotoxicity by reducing oxidative stress (69).

PARP inhibitors

Poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib are indicated for metastatic breast cancer. There is a 14% increase in serum creatinine following Olaparib use. However, a detailed study showed that this increase in serum creatinine is a result of kidney transporter inhibition rather than declining GFR. It is dose-dependent and reversible (70).

PD1/PD-L1 inhibitor

In 2019, the FDA approved atezolizumab, an immune checkpoint inhibitor (ICI), for unresectable locally advanced or metastatic triple-negative breast cancer (71). Approximately 1-4% of patients receiving atezolizumab or other PD1/PD-L1 inhibitors develop acute kidney injury. Therefore, it is important to monitor serum creatinine and GFR in these patients regularly before and after treatment with atezolizumab (72,73). Another paper reported progressive pauci-immune GN following atezolizumab. In this case, the renal injury was partially reversible after two weeks of conservative treatment (74).

Monoclonal antibodies

Trastuzumab is a human monoclonal antibody designed for the treatment of HER2-positive breast cancer (75). The FDA adverse effects reporting system has reported a 10% prevalence of renal side effects with trastuzumab. However, we did not find any published reports on the exact cases of trastuzumab-induced renal insufficiency (76). There is a report of collapsing FSGS and tubular damage following ado-trastuzumab emtansine therapy, which is a conjugation of trastuzumab with the antineoplastic maytansinoid DM1. However, it has not been identified that trastuzumab, DM1, or a combination of both is responsible for this adverse effect (77).

Calcium metabolism modifiers

Bisphosphonates are complementary to breast cancer hormonal therapy and chemotherapy; they may reduce bone damage in metastatic disease by inhibiting osteoclast activity (78). Pamidronate may cause kidney damage mainly by developing nephrotic syndrome and FSGS, while zoledronate is a more potent bisphosphonate that contributes to renal tubular injuries. These renal side effects are more common in patients receiving IV forms and higher doses. Since an IV form of bisphosphonate is indicated in malignancies rather than osteoporosis, its nephrotoxicity has not been reported in patients who receive oral agents for osteoporosis treatment. Regular urine albumin and serum creatinine monitoring are recommended to stop the development of renal damage (79). Ibandronate is believed to be safer than other bisphosphonates in terms of acute kidney damage. This is acceptable at lower doses. However, in breast cancer

patients who often need higher doses of bisphosphonates, there is a lower difference between the nephrotoxicity of ibandronate and that of other bisphosphonates (80,81).

Radiation therapy

Radiation therapy is another part of the breast cancer treatment protocol, which improves outcomes and increases the survival of patients. There are different techniques used in breast cancer radiotherapy. Techniques are rapidly changing to achieve the best prognosis. Whole breast radiotherapy plus targeted nodal irradiation is the gold standard in breast cancer radiation treatment. Partial breast irradiation is used instead in selected patients (82,83). Since radiation is usually limited to the breast and axillary lymph nodes, there is a lower chance of radiation nephritis in breast cancer patients compared to other malignancies. However, with metastatic breast cancer, rules are changing; there are patients with metastatic disease in the abdominopelvic area who need symptomatic radiotherapy (84-86). In such cases, radiation to the kidneys in the treatment course of breast cancer seems to be possible and should be considered.

There is a 6-month-long latent period before radiation nephritis symptoms appear in the patient. Hence, clinicians should keep this possibility in mind, or they will miss some patients' true etiology of nephritis. The first clinical features of radiation nephritis are seen in the acute phase (6-18 months) after radiotherapy. Chronic radiation nephritis may occur after 18 months. Oxidative stress, DNA damage, RAAS activation, inflammation, and fibrosis are mechanisms that affect renal function after radiation (87).

Lowering the radiation dose as much as possible, proper shielding, regular renal function monitoring, the use of angiotensin receptor inhibitors (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs), the use of radioprotective agents and adequate hydration are strategies to reduce radiation nephritis (88, 89).

Breast cancer in patients with reduced renal function

Chronic kidney disease can be a challenging condition in a patient who is under breast cancer treatment. Furthermore, the possible relationship between CKD and breast cancer needs to be determined. Here, we tried to highlight the major concerns in the incidence, disease course, and treatment of breast cancer patients with reduced GFR.

Shreds of evidence suggest that cancer is more common among CKD patients. The increased cancer incidence in such patients may be due to chronic inflammation, toxin accumulation, and higher oxidative stress (10,11,90,91). Nevertheless, if we specify primary cancer types in the CKD patient population, no increased risk is detectable for breast cancer and surprisingly it occurs less commonly in female CKD patients than in other females. A shorter longevity and risk underestimation can explain this

paradoxical finding. More investigation and larger studies in the future may reveal the true impact of CKD on developing breast cancer. Currently recommended breast cancer screening protocol for CKD patients is similar to that for the normal population (92,93).

CKD also affects breast cancer outcomes. It is an independent mortality risk factor for all cancer types including breast cancer (94,95). Ishii T et al found an association between CKD and increased mortality in stage IV breast cancer patients (96). Renal insufficiency increases the incidence rate of potentially fatal complications such as venous thromboembolism (VTE) in breast cancer patients. Clinicians should consider this increased risk, particularly before endocrine therapy begins (97,98).

To limit the renal and extrarenal side effects of chemotherapeutic agents, dose adjustment according to the patient's renal function (GFR) is crucial. Addressing the proper drug adjustment for all of these medications is not discussed in this paper. GFR assessment before and during the treatment course is strongly recommended for patients. Time adjustment between dialysis sessions and drug intake is the key to avoiding unwanted drug elimination (99).

Conclusion

In conclusion, there are many aspects to consider in the association between breast cancer and renal insufficiency. A breast cancer patient with normal kidney function is at risk of developing kidney failure due to paraneoplastic syndromes, hypercalcemia, and in rare cases, tumor lysis syndrome (TLS). In defining the optimal treatment protocol for each breast cancer patient, clinicians should consider the patient's basal GFR. Frequent renal clearance monitoring and taking immediate action at the time GFR begins to decrease will lower the rate of kidney failure in breast cancer patients. Lastly, patients with CKD who are recently diagnosed with breast cancer may have higher morbidity and mortality compared to breast cancer patients with normal GFR. Further investigation is needed to lower morbidity and mortality in such patients.

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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