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REVIEW

Systemic oncological therapy in breast cancer patients on dialysis

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Abstract

The advancement of renal replacement therapy has significantly enhanced the survival rates of patients with end-stage renal disease (ESRD) over time. However, this prolonged survival has also been associated with a higher likelihood of cancer diagnoses among these patients including breast cancer. Breast cancer treatment typically involves surgery, radiation, and systemic therapies, with approaches tailored to cancer type, stage, and patient preferences. However, renal replacement therapy complicates systemic therapy due to altered drug clearance and the necessity for dialysis sessions. This review emphasizes the need for optimized dosing and administration strategies for systemic breast cancer treatments in dialysis patients, aiming to ensure both efficacy and safety. Additionally, challenges in breast cancer screening and diagnosis in this population, including soft-tissue calcifications, are highlighted.

Key Words: Breast cancer; Systemic therapy; Renal replacement therapy; Dialysis; End-stage renal disease; Hormone therapy; Chemotherapy

Core Tip: Optimizing systemic breast cancer therapy in dialysis patients requires tailored approaches due to altered drug clearance and dialysis sessions' necessity. This review emphasizes the significance of optimizing dosing and administration strategies, ensuring both efficacy and safety. Challenges in breast cancer screening, including soft-tissue calcifications, are highlighted, underlining the necessity for precise diagnostic strategies in this population. Furthermore, nuanced understanding and guidelines are imperative to navigate the complexity of oncological treatment in dialysis patients, ultimately enhancing patient outcomes.

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INTRODUCTION

The number of patients with end-stage renal disease (ESRD) worldwide has increased rapidly over the past few decades. With the development of renal replacement therapy, patients with ESRD have had improved survival with time[1], which increased their likelihood of being diagnosed with various cancers over time and increased the incidence of various malignancies in this population[2-5]. In a study conducted in northeastern Italy, the risk of developing *de novo* malignancies was 1.3 times greater in the dialysis group than in the general population. This increased risk was particularly notable for certain types of cancer, including nonmelanoma skin cancer, kidney cancer, oral cavity cancer, and Kaposi's sarcoma[6].

Breast cancer is the most common cancer worldwide[7]. Some studies have shown an increased risk of breast cancer in dialysis patients[8]. According to the United States Renal Data System, in the years 1996-2009, 3552 women on hemodialysis (HD) were diagnosed with breast cancer, which is 42% higher incidence than in the general population[5]. A prospective cohort study with a median follow-up time of 12.8 years explored cancer mortality instead of incidence. Compared with participants with an estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m^2, the hazard ratio (HR) for breast cancer death for women with an eGFR < 60 mL/min/1.73 m^2 was 1.99 (95% confidence interval: 1.05- 3.85; P = 0.01) after adjusting for age, smoking status, and employment status. This increase in mortality was attributed to a few different reasons. First, patients with ESRD often have multiple other medical comorbidities, the management of which can lead to route cancer screening not being a priority. Second, adjusting the dose of cytotoxic agents for patients with reduced kidney function can be challenging, and therefore, treatment can be suboptimal. Third, patients with ESRD may have more aggressive breast cancer, given the state of chronic inflammation induced by continuous exposure to oxidative stress (leading to tumor proliferation) and uremia (accentuating mitogenesis)[9]. Although ESRD has not been proven to be a risk factor for breast cancer, it has a significant impact on its therapy because it drastically changes the pharmacokinetics of cytotoxic drugs and other systemic agents used in breast cancer treatment.

Surgery, radiation, and systemic therapies are the mainstay of the treatment of breast cancer. The specific treatment approach is usually tailored based on the type and stage of cancer, the patient's health status, and personal treatment preferences. Surgical intervention in breast cancer management is primarily focused on the excision of malignant tissue, and it can be preceded or followed by chemotherapy, radiation therapy, or both. Radiation therapy employs potent energy beams to destroy or inhibit cancer cell growth and encompasses external and internal radiation therapy[10]. Systemic therapies are designed to target cancer cells throughout the body and can be administered as adjuvant, neoadjuvant, or palliative treatment. The primary categories include chemotherapy, hormone therapy [used in estrogen and progesterone receptor (PR)-positive cancers], anti-human epidermal growth factor receptor 2 (HER2) therapy, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, poly ADP-ribose polymerase (PARP) inhibitors, and immunotherapy[11,12]. When treating breast cancer patients with ESRD, renal replacement therapy does not limit the utility of surgical treatment and radiotherapy; however, it significantly impacts systemic therapies due to the reduction or loss of renal clearance of drugs and their metabolites and their elimination during dialysis sessions. This alteration of pharmacokinetics significantly affects the dosage and timing of administration of these drugs in dialysis patients.

The purpose of this review is to highlight current knowledge on systemic treatments used in the adjuvant, neoadjuvant, and palliative treatment of breast cancer in dialysis patients. It highlights the existing research on recommended dose modifications and timing of these medications' administration about dialysis in this specific group of patients to guarantee the most effective and safe treatment of breast cancer. It also sheds light on the challenges faced in breast cancer screening and diagnosis in this population due to soft-tissue calcifications.

IMPLICATIONS OF SOFT-TISSUE CALCIFICATIONS IN ESRD ON BREAST CANCER SCREENING

Patients with chronic kidney disease (CKD) and ESRD are known to develop soft-tissue calcifications in multiple tissues, including the breast, mainly secondary to hyperparathyroidism[13-15]. This can pose challenges in breast cancer screening in this population. They often develop vascular calcifications, which may be dense areas on mammograms and mimic the appearance of breast microcalcifications, making distinguishing between benign and malignant findings

difficult. This may lead to false positive or false negative findings in breast cancer screening in this population. False positives can result in unnecessary workups and interventions, while false negatives may lead to delayed diagnosis and treatment[16-18]. The investigation of this issue is critical in order to provide high-quality, precise breast care to women with CKD or ESRD, yet there is currently little evidence available.

Studies have shown that breast vascular calcifications increase with the progression of CKD[19]. However, data on the morphological characteristics of breast calcifications in this population, the incidence of benign *vs* malignant calcifications, and their clinical implication are limited. Castellanos *et al*[20] reviewed the mammograms, traced the recommended workup of women on HD, and compared it to that of women with normal renal function. The incidence of calcifications was higher in HD patients but was attributed mainly to benign calcification patterns. Vascular calcification was the most common pattern in both groups when comparing the categories of benign calcifications. At the same time, HD patients were likelier to have other calcification patterns, including parenchymal spherical and lucent calcification patterns. However, even when comparing the incidence of calcifications commonly considered to be associated with malignancy (BI-RADS 4 and 5) prompting biopsy, patients on HD had significantly higher incidence and a greater probability of being recommended for biopsy.

Further studies with a large sample size are recommended to investigate the incidence, morphologic characteristics, and clinical implications of breast calcifications in HD patients to direct screening and biopsy recommendations in this population. At this time, mammography remains the gold standard for screening breast cancer in women on dialysis. Clinicians managing these patients should be aware of the increased incidence of calcifications and the risk for further workup and interventions in these patients.

SYSTEMIC THERAPIES

In the context of treating breast cancer in patients with ESRD on HD, the selection and administration of chemotherapeutic agents are marked by a significant degree of complexity and confusion. This stems mainly from the altered pharmacokinetics in these patients, necessitating careful consideration of drug metabolism and renal clearance. The decision-making process is further complicated by the need for potential dose adjustments and the impact of renal function on drug efficacy and toxicity. While hormone therapies and other systemic treatments offer additional options, their use in the ESRD population also requires a nuanced understanding of their interaction with renal dysfunction. The current scenario highlights a critical need for more comprehensive research and precise guidelines to navigate the intricacies of oncological treatment in this unique patient group. This would enable healthcare providers to optimize therapy, balancing efficacy and safety and ultimately improving patient outcomes in breast cancer patients undergoing HD.

Hormone therapies

Approximately 20%-30% of breast cancers express hormone receptors, including estrogen receptors (ERs) and PRs. Hormone receptor-positive breast cancers depend on these hormones for growth and spread. Various hormone therapy agents are used to treat these hormone receptor-positive breast cancers. However, prescribing these agents for dialysis patients is unique because of alterations in drug metabolism and the high pill burden often associated with dialysis.

Tamoxifen

Tamoxifen is a selective ER modulator that works by inhibiting estrogen's action on breast cancer cells. It is often used for premenopausal women or those with contraindications to aromatase inhibitors (AIs). The CYP2D6 and CYP3A4 enzymes metabolize tamoxifen into more potent metabolites[21]. The drug avidly binds (95%) to proteins and has high lipophilicity. It is metabolized by cytochrome P450 enzymes in the liver, forming 4-hydroxy tamoxifen and N-desmethyltamoxifen. Approximately 60 % of the drug is excreted unaltered in feces and 9%-14% in the urine. The plasma level of tamoxifen remains constant for 3-4 weeks when it is daily dosed at 20-40 mg once a day. It is noted that the half-life of the drug is 5-7 days, while the metabolite N-desmethyl tamoxifen needs 13 days to be cleared from the body[22]. The study by Langenegger *et al*[23] described that the use of tamoxifen in an HD does not need any dose adjustments. The plasma concentration of the drug was similar in HD patients compared to non-HD patients. It is advisable that due to the drug's high lipophilicity, it should be administered before the HD session. However, concomitant medications used in dialysis may inhibit these enzyme systems, leading to reduced efficacy of tamoxifen. Close monitoring is required if this approach is used in dialysis patients.

AIs

This group of drugs includes anastrozole, letrozole, and exemestane. These drugs work by suppressing estrogen production and achieving the estrogen deprivation state in a postmenopausal woman. AIs are preferred over tamoxifen for treating postmenopausal women with hormone receptor-positive breast cancer[24].

Anastrozole is a common drug for breast cancer in early and metastatic cancer stages. It is 40% bound to plasma proteins. The liver is responsible for 85% of its metabolism and excretes into feces, but only 11% of the total drug is excreted by the kidneys. The study by Langenegger *et al*[23] mentioned that the half-life of the drug is 41 hours. According to the same study, the serum concentration of anastrozole in patients on HD is similar to those seen in patients with normal renal function. Therefore, it does not need any dose adjustment in patients with HD. However, due to low molecular mass and strong affinity for plasma proteins, it is advisable to take the drug after an HD session.

Exemestane avidly binds to proteins (90%) and is inactivated by the liver, which means the metabolites are not biologically active. It is noted that only a small portion of the drug, which accounts for 1%, is excreted unaltered in the urine. For individuals with creatinine clearance (CC) below 30 mL/min, the extent of exemestane absorption, shown by the area under the curve (AUC), is twice as much as that in individuals with normal kidney function. There are no specific guidelines on the administration and safety of this medication for patients with a GFR below 30 mL/min/1.73 m^2, including patients on renal replacement therapies. Therefore, dose adjustments for patients with CKD are not recommended, but extreme caution is advised when administering the drug to patients undergoing dialysis. It is preferable to avoid the drug and use other alternative options if available; otherwise, exemestane should be used as a last resort in that scenario[25].

Similarly, letrozole, an AI, is changed into its inactive metabolite (carbinol) in the liver by (isoenzymes: 3A4, 2A6 of cytochrome P450)[23]. The characteristics of the drug show that it does not need any dose adjustment for patients with CKD and CC greater than 30 mL/min. There is no data on patients with CC < 30 mL/min. There is a single clinical report on a patient treated with Letrozole and lapatinib for breast cancer on HD; the therapy was well tolerated without adjusting the dosage[26].

Fulvestrant

Fulvestrant is another ER-directed agent that works differently from tamoxifen or AIs. It is a selective ER down regulator with no agonist effects. It is highly bound to plasma lipoproteins (99%), is metabolized very slowly in the liver *via* the same pathways as endogenous steroids, and is excreted into feces[27]. Although CYP3A4 metabolizes fulvestrant, pharmacokinetic studies have shown that dialysis patients may not require dose adjustments. The biological half-life of the drug is estimated to be 40 days. No data on the drug's safety and pharmacokinetics in dialysis patients is available. Due to the limited role of the kidney in its elimination process, the drug can be used in ESRD patients on HD in unchanged doses. Hence, this approach may benefit patients unsuitable for other hormone therapies[28].

Megestrol acetate

Megestrol acetate is a synthetic progestin that has anticachectic as well as antineoplastic effects and is used in the treatment of advanced breast cancer with disease progression[29]. The drug has high affinity to bind albumins and there is limited role of the kidneys in its excretion process. The liver slowly metabolizes the drug, and its metabolites are excreted into feces. Megestrol acetate has been evaluated in numerous trials for its safety in dialysis patients and it can be used in the therapy of metastatic breast cancer in this population[30].

CDK 4/6 inhibitors

More recently, CDK 4/6 inhibitor drugs such as (palbociclib, ribociclib, and abemaciclib) have been introduced for hormone receptor-positive metastatic breast cancers. These agents enhance the efficacy of antiestrogen drugs. These drugs undergo significant hepatic metabolism *via* CYP3A enzymes. All the CKD 4/6 inhibitors are protein-bound molecules metabolized in the liver by cytochrome P450 isoenzymes and are excreted into feces. Although no studies are available yet, according to the drug's pharmacokinetics, there is no need to reduce the dose of the drug in CKD/ESRD patients on HD. On the contrary, these drugs may have some nephroprotective effects by inhibiting the CDK4/6 pathway and have been shown to decrease kidney injury caused by cisplatin[31]. It is essential to mention that in approximately 40% of the individuals, abemaciclib is associated with a reversible increase in serum creatinine concentration greater than 50% over the baseline levels[32]. The drug inhibited renal tubular secretion of creatinine without changes in the measured GFR and the structural markers of kidney tubular injury[33].

CHEMOTHERAPEUTIC AGENTS

Cyclophosphamide

Cyclophosphamide (CTX), a frequently utilized chemotherapeutic drug, affects various cell functions. Its therapeutic efficacy is contingent upon metabolic activation, predominantly in the liver. This activation is facilitated by P450 isoenzymes, which convert P450 into its active derivatives, phosphoramide mustard, which contributes to cancer-fighting capabilities, and acrolein, which is known for its toxicity and potential link to bladder cancer[34]. Notably, the ability of CTX to suppress immune functions, including reducing lymphocyte counts and inhibiting the activity of both T cells and B cells, accounts for its application in treating certain autoimmune disorders and preventing organ rejection in transplant recipients.

Approximately 50% to 70% of CTX is excreted by kidneys within 48 hours, with approximately 32% expelled in its unchanged form. The exploration of CTX in patients undergoing dialysis has been limited, yet some noteworthy examples exist in the literature. For example, a case study reported a 48-year-old woman with breast cancer who was receiving HD[35]. The study revealed that the peak plasma concentration of CTX was approximately 49 μg/mL and the *in vivo* half-life of the drug extended to 67 hours. Based on these findings, it is evident that CTX is dialyzable and, as such, should preferably be administered post-HD sessions or on days when dialysis is not scheduled. In another study, CTX was administered intravenously at a dose of 0.5-1 g/m^2 for 1 hour in HD patients; an HD session was done 7 hours after administration. Mean CTX clearance was moderately lower in HD patients than in patients with normal renal function. The AUC was increased in HD patients. Thus, it is necessary to reduce the dose of CTX by 25% in HD patients[36].

Two-drug regimen: AC/EC

Anthracyclines, particularly doxorubicin (doxorubicin; also known as adriamycin), function as antibiotics that interfere with DNA by disrupting topoisomerase-II activity and generating free radicals. These processes hinder DNA replication and transcription, ultimately leading to cellular death. A known side effect of doxorubicin is cardiotoxicity, necessitating regular monitoring through echocardiography for patients receiving this treatment.

The regimen is typically administered every two to three weeks over several cycles, and the frequency and duration of the anthracycline regimen, including doxorubicin, depends on multiple factors, such as the stage and specific type of breast cancer. Research on the pharmacokinetics of doxorubicin in patients with renal insufficiency is sparse, presenting challenges in understanding its efficacy and safety in this population. Both doxorubicin and its primary active metabolite doxorubicinol are cleared renally.

Its efficacy is enhanced by its ability to target cancer cells *via* diverse mechanisms, increasing potential side effects. For patients undergoing HD, there are specific guidelines for the anthracycline regimen, particularly for patients receiving doxorubicin. A reduction in the doxorubicin dose of 20%-25% is generally considered safe for patients with CKD/ESRD, including those receiving HD treatment. In dual-drug regimens for HD patients, administering these medications on nondialysis days is advised to ensure optimal treatment efficacy and safety[37].

Paclitaxel and docetaxel

Paclitaxel and docetaxel, which are part of the taxane family of chemotherapeutic drugs, are utilized in treating a variety of cancers, such as breast, ovarian, lung, and prostate cancer. Paclitaxel's mode of action involves stabilizing cellular microtubules, which are crucial for cell division, thereby inducing cell death, particularly in fast-dividing cancer cells[38]. A notable side effect of paclitaxel is peripheral neuropathy, characterized by numbness and pain. Additionally, it can cause neutropenia, hair loss, and hypersensitivity reactions, the latter often linked to its formulation. Both drugs strongly bind to proteins such as albumin and alpha-1-glycoprotein. These drugs are metabolized predominantly in the liver *via* the cytochrome P450 system, followed by excretion primarily into the bile and, to a lesser extent, in the urine[39].

Studies indicate that the pharmacokinetics of a standard dose of paclitaxel (135 mg/m^2 administered over three hours intravenously) in patients on HD mirrors those with normal renal function[40]. These findings suggested that renal function does not significantly impact the elimination of the drug. The typical dosage for breast cancer treatment with paclitaxel is 80 mg/m^2 administered weekly. Additionally, docetaxel has shown good tolerability in a 72-year-old patient with prostate cancer undergoing HD[41]. Furthermore, Watanabe *et al*[40] reported the safe and practical application of paclitaxel in a 40-year-old woman on HD.

Gemcitabine

Gemcitabine, a key chemotherapeutic drug, is crucial in the treatment of various solid tumors, including breast cancer. It functions as a deoxycytidine analog and disrupts DNA synthesis. This disruption occurs when gemcitabine integrates into DNA during the S phase of the cell cycle, leading to an interruption in the DNA chain. Metabolically, gemcitabine is transformed into active forms, namely, diphosphate and triphosphate nucleosides[42]. The diphosphate form is essential because it inhibits ribonucleotide reductase, an enzyme critical for synthesizing deoxyribonucleotides. Inhibiting this enzyme *via* gemcitabine leads to a reduced pool of deoxynucleotides, thus hindering DNA synthesis. This sequence of events triggers apoptosis in cancer cells. The drug's effectiveness is also augmented by a self-enhancing mechanism that increases its uptake into cells and integration into DNA, mainly by inhibiting ribonucleotide reductase.

Regarding metabolic processing, gemcitabine primarily undergoes processing in the liver, with limited renal involvement, as only a minor portion is bound to plasma proteins and undergoes renal filtration. In conjunction with HD, the kidneys facilitate the removal of the primary nontoxic metabolite difluorodeoxyuridine. Significantly, in patients with CKD and ESRD, administering gemcitabine at doses up to 1200 mg/m^2 did not differ in toxicity or pharmacokinetics compared to that in individuals with normal renal function, indicating that adjusting the dosage for CKD/ESRD patients on HD may not be essential[43].

Carboplatin

Carboplatin, a chemotherapeutic agent that is a platinum compound, is extensively utilized in treating numerous cancer types, including breast cancer. It resembles cisplatin but is differentiated by its unique toxicity profile. The primary anticancer action of carboplatin involves the formation of crosslinks within DNA, thereby disrupting both DNA replication and transcription processes, which is particularly effective against rapidly multiplying tumor cells. This agent's impact is not limited to a specific phase of the cell cycle, allowing it to affect cancer cells at various stages of growth. It is notably efficacious in the treatment of triple-negative breast cancer (TNBC), a subtype devoid of estrogen, progesterone, and HER2/neu receptors[44].

Carboplatin is administered intravenously and remains unbound mainly in the bloodstream initially but predominantly binds to proteins within 24 hours. Approximately 55%-70% of the drug is eliminated by the kidneys within the first 24 hours[44]. Carboplatin is considered safe for individuals with a CC above 20 mL/min, although dosage adjustments are required when the CC is less than 60 mL/min to avoid myelotoxicity[45]. In cases of renal impairment, the Calvert formula is typically used for dosage calculations, aiming for a specific AUC[46]. Although not standard practice, dialysis patients may receive reduced carboplatin doses. The AIOM guidelines recommend adjusting an AUC × 25 mg dosage for HD patients[37].

To ensure efficient removal, HD and peritoneal dialysis (PD) should be carried out within 12-18 h after carboplatin infusion before binding to proteins, decreasing dialysis. Research by Hiraike *et al*[47] showed that standard doses of carboplatin, as per the Calvert formula, maintain predictable pharmacokinetics if HD is initiated one hour after adminis-

tration. In PD patients, such as those undergoing continuous ambulatory PD, approximately 20% of carboplatin is removed *via* dialysate, and its half-life is extended compared to that of patients with normal kidney function[48]. Although ideally administered on dialysis days just before the session, current protocols often suggest giving carboplatin on non-dialysis days for logistical reasons[37].

Fluorouracil

5-fluorouracil (5-FU), a molecular entity weighing 130 Da, is a pyrimidine antimetabolite used in chemical treatment. The mechanism of action of 5-FU lies in its structural resemblance to uracil and thymidine, fundamental elements of RNA and DNA. It undergoes metabolic conversion into substances interrupting RNA and DNA synthesis[49]. A key metabolite, fluorodeoxyuridine monophosphate, inhibits explicitly thymidylate synthase, which is crucial for synthesizing the thymidine necessary for DNA replication. This inhibition results in a thymidine deficit, disrupting DNA synthesis and leading to the death of rapidly multiplying cancer cells. Simultaneously, the presence of 5-FU metabolites in RNA affects standard RNA processing. Despite its efficacy in cancer treatment, 5-FU has a range of side effects. Myelosuppression is frequently observed, which can lead to reduced blood cell counts and increased risks of infection, anemia, and bleeding. Gastrointestinal discomfort, such as nausea, diarrhea, and mucositis, are other common side effects. Cardiotoxicity, manifesting as chest pain or irregular heartbeats, and neurotoxic symptoms such as confusion or lack of coordination are also associated with 5-FU therapy.

Its half-life averages approximately 16 minutes when administered intravenously, although this can vary depending on the administered dose. Notably, a mere 15% of the administered 5-FU is eliminated *via* the urine in its original form. In the context of end-stage kidney disease (ESKD), the standard protocol involves administering 5-FU doses after HD sessions or on days without dialysis, considering the modified excretion patterns in such patients. Given these potential adverse effects, careful monitoring and dosage adjustments are imperative to ensure a safe balance between the drug's effectiveness and patient well-being, particularly in those with impaired renal function[50].

Capecitabine

Capecitabine, with a molecular weight of 359.3 Da, is a precursor to 5-FU. Expanding on this mechanism, Capecitabine is metabolized in the liver and converted into 5-FU at the tumor site through a three-step enzymatic process. The enzyme thymidine phosphorylase facilitates the final step and is more abundant in tumor cells than in normal cells, allowing targeted drug action. The active form, 5-FU, subsequently inhibits thymidylate synthase, disrupting DNA synthesis and repair and leading to cancer cell death. Capecitabine is a targeted cancer treatment, but it can also result in several side effects. Apart from the myelosuppression above and gastrointestinal disturbances, patients might experience alopecia, dermatological reactions, and, in some cases, cardiotoxicity, which necessitates careful dose management and vigilant medical supervision. Such side effects underscore the importance of individualized treatment planning, especially for patients with compromised renal function[51].

This prodrug is processed and excreted mainly through renal pathways, with 96% of its dosage identifiable in the urine. The utilization of capecitabine in patients with advanced CKD or ESKD, particularly those undergoing HD, has been explored in limited clinical studies. One notable investigation by Jhaveri *et al*[52] included 12 participants with severe CKD or ESKD (with a CC less than 30 mL/min), among whom two received HD and were administered capecitabine. This cohort exhibited minimal toxicity, indicating the relative safety of the drug. For ESKD patients, the regimen typically involves a dosage reduction to approximately 55% of the standard amount. Despite such dose modulation, patients showed a favorable response to the treatment. The research also examined the pharmacokinetics of capecitabine, recommending a 50% reduction in dosage for similar patients[52]. Given the lack of data and the need for dosage adjustments, stringent monitoring of adverse effects such as myelosuppression, hand-foot syndrome, and diarrhea is imperative after the commencement of treatment.

Methotrexate

Methotrexate (MTX) operates by targeting and inhibiting the enzyme dihydrofolate reductase, which is crucial in the folic acid metabolic pathway. This pathway is essential for producing the building blocks of DNA and RNA, such as purines and pyrimidines. By blocking dihydrofolate reductase, MTX reduces tetrahydrofolate, disrupting DNA, RNA, and protein synthesis. This disruption mainly affects rapidly dividing cells, such as cancer cells. In addition to its use in treating cancer, MTX is also used for treating certain autoimmune conditions due to its ability to diminish inflammatory responses[53].

The broad action of MTX on cell division also accounts for its side effects. These include gastrointestinal discomfort, manifesting as nausea or vomiting, mucositis, or inflammation of the mucous lining. Its impact on the bone marrow can lead to myelosuppression, resulting in diminished blood cell production and elevated risks of infection, anemia, and bleeding complications. Prolonged usage might contribute to liver damage, as indicated by increased liver enzymes, and potentially advance to fibrosis or cirrhosis in severe instances. Although less frequent, pulmonary issues such as breathlessness or persistent cough can signify pulmonary toxicity. Renal effects are also noteworthy, particularly at higher dosages, as they can cause an accumulation of the drug, heightening its toxic effects. This necessitates vigilant monitoring and potential dose modifications, especially in individuals with renal challenges[53].

MTX, with a molecular weight of 454.4 Da, is a derivative of folic acid and is an antimetabolite. Its elimination is primarily renal-based and depends significantly on the administered dose and the method of administration. When given intravenously, approximately 90% of MTX is excreted unchanged from the body within the first day, and less than 10% is biliary excreted. With the aid of aldehyde oxidase, the liver produces the significant metabolite 7-hydroxy MTX. For patients receiving lower doses of MTX (under 30 mg/m^2), the drug's half-life in the final elimination phase ranges from 3

to 10 hours. However, this extends to 8 to 15 hours in those receiving higher doses. The interaction of MTX with other drugs that target other excretion pathways can elevate its serum concentrations. Notably, nonsteroidal anti-inflammatory drugs can affect the renal clearance of MTX, potentially leading to increased toxicity. High-dose MTX, which is used in hematology (up to 6 g/day), can cause adverse drug reactions (ADRs), such as hematuria and acute kidney injury. MTX metabolites may crystallize in the renal tubules during therapy. To counter this, strategies such as intensive hydration and urine alkalization (targeting a pH of 6.5-7.0) are employed, for instance, using sodium bicarbonate or acetazolamide, less preferably in CKD. Acute renal failure, a risk factor particularly at doses exceeding 1000 mg/m^2, can impair MTX elimination, exacerbating ADRs, the likelihood of which increases with dosage[54].

In breast cancer therapy (such as the CMF regimen), the MTX dose is generally lower. However, cases such as the one reported by Langleben *et al*[55] show severe toxicity after initial administration in breast cancer treatment. Reducing this toxicity may be achieved through high-flux dialysis conducted daily[56]. In patients with ESKD, the use of MTX is advised against if alternatives are available. In HD patients, a 75% dose reduction is recommended[37].

Anthracyclines

The guidelines from the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology, and American Society of Clinical Oncology suggest that patients who have ER+/PR+/HER2+ invasive breast cancer and positive lymph nodes should undergo an adjuvant chemotherapy regimen that includes anthracycline and CTX, followed by taxanes and trastuzumab (AC to TH)[36]. The anthracyclines commonly used in breast cancer chemotherapy include doxorubicin and epirubicin[57].

The production of hydroxyl free radicals by anthracyclines is linked to both anticancer properties and potential harm to healthy tissues. The primary adverse effects that limit the dosage of anthracyclines include acute myelosuppression and cumulative dose-related cardiotoxicity. Cardiomyopathy induced by anthracyclines is often irreversible, potentially leading to clinical congestive heart failure[58]. Doxorubicin and epirubicin are removed mainly by the liver and, to a lesser degree, are excreted by the kidneys (15% and 10%, respectively)[59]. Data on the pharmacokinetics of doxorubicin in patients with renal insufficiency are currently limited[41]. Since doxorubicin and its primary active metabolite, doxorubicin, are not predominantly excreted, the dose of doxorubicin should not be modified in renal insufficiency patients[60].

Although the AUCs of doxorubicin and doxorubicin are greater in renal insufficiency patients than in patients with normal renal function, the half-lives of these two compounds are the same in both patient groups[61]. Therefore, dose reduction of doxorubicin in dialysis patients is not recommended[37]. There are currently limited data on epirubicin pharmacokinetics in ESRD patients on HD. Although dose reduction should be considered in patients with a CC < 30 mL/min, studies on the effectiveness of a reduced dose are limited[59]. A case report presented by Gori *et al*[62] described a patient with early breast cancer on HD who tolerated epirubicin without any adverse effects, including leukopenia, thrombocytopenia, or cardiotoxicity.

Cisplatin

Cisplatin belongs to platinum drugs that alkylate DNA by forming platinum-DNA adducts, leading to DNA damage, G1/S arrest, and apoptosis[63]. Cisplatin is not routinely used for breast cancer treatment, and the feasibility of cisplatin-based regimens has been confirmed in non-breast cancer patients. There is currently no data concerning the safety and efficacy of cisplatin in dialyzed breast cancer patients[59]. However, cisplatin can be an effective therapy for hereditary BRCA-1-mutated breast cancer and sporadic TBNC because they share features suggesting common pathogenesis[64]. Despite not being a standard therapeutic option for TBNC at present, there is growing interest in the potential of cisplatin, with 22 active clinical trials investigating its use, either as a standalone therapy or in combination with other treatments[65]. Although cisplatin has been available for more than 40 years, we are still struggling with severe dose-limiting side effects, particularly nephrotoxicity, which can affect dosing in approximately 30%-40% of patients[66]. The nephrotoxicity caused by cisplatin is dose-dependent, and the renal failure it induces, typically manifesting as acute tubular necrosis, is often reversible[13]. However, there are case reports in which patients developed permanent renal failure after the use of neoadjuvant cisplatin[67]. Cisplatin is predominantly eliminated through the kidney (approximately 90%)[37]. Although the use of cisplatin in patients with CKD should be avoided, it may still be used for patients with ESRD on dialysis[59]. Dose adjustments must be made in patients with ESRD on dialysis due to Cisplatin's ability to form solid and irreversible bonds with plasma proteins[37]. Tomita *et al*[68] recommended dose adjustment and administration immediately before dialysis sessions. In contrast, since the rapid elimination of free cisplatin during dialysis is not compensated by the portion of the drug complexed with protein, Janus *et al*[41] recommend administering a reduced dose of 25%-50% after dialysis.

Vinorelbine

Vinorelbine is an antimitotic anticancer agent, and its primary mechanism of action is related to the inhibition of microtubule dynamics, leading to mitotic arrest and cell death[69]. Combination chemotherapy comprising vinorelbine and doxorubicin has demonstrated effectiveness in treating advanced breast cancer, yielding response rates between 57% and 74% when used as first-line therapy[70]. The drug is eliminated mainly through the liver; only 8% of the administered dose is recovered unchanged from the urine. Vinorelbine is mainly eliminated through the liver, with only 8% of the administered dose recovered unchanged from the urine[71].

However, the superior efficacy of paclitaxel and docetaxel has led to taxane and anthracycline-based chemotherapies becoming the standard first-line treatment for metastatic breast cancer[70]. Janus *et al*[41] recommended reducing the initial dose of vinorelbine to 20 mg/m^2/week. The pharmacokinetic data associated with vinorelbine in HD patients have

not been studied; therefore, administering vinorelbine after HD sessions or on non-dialysis days is recommended.

HER-2 BASED THERAPIES

Approximately 20% of early breast cancers express HER2, and more than half of these patients are expected to progress without HER2-targeted therapy[72]. HER2-directed therapies have improved survival.

Anti-Her2 monoclonal antibodies and conjugates

Trastuzumab: Trastuzumab is a recombinant monoclonal antibody that binds the extracellular domain of HER2. Trastuzumab binds to HER2 receptors on breast cancer cells, leading to downstream heterodimerization, phosphorylation pathways, and ultimately, cell cycle arrest through AKT inhibition and antibody-dependent cell cytotoxicity in HER2-overexpressing breast cancer cells[73,74]. The efficacy of trastuzumab is comparable to that of endogenous immunoglobulins (Igs). It has low systemic clearance, a low volume of distribution, a long half-life (about 28 days), and little to no known drug-drug interactions. It is cleared by the Fc receptor-mediated IgG clearance mechanism[75,76].

Cardiotoxicity is a known concern associated with trastuzumab use and remains the primary reason for trastuzumab discontinuation in patients[77]. To our knowledge, there are no reports of trastuzumab-induced nephrotoxicity, although cases have been reported when trastuzumab was combined with other chemotherapeutic agents[78]. The product label suggests no dosage adjustment for mild to moderate renal dysfunction. Although no information exists regarding dosage adjustment in HD patients, this treatment is well tolerated in chronic renal failure and ESRD patients on HD[76,79,80] After analysis of the Food and Drug Administration adverse event reporting system, renal events (10%) included proteinuria, acute kidney injury, elevated serum creatinine, and electrolyte imbalances. However, whether such events were from concurrent or prior chemotherapy was unclear. Russo *et al*[81], in a study including 499 patients with ERB2+ early breast cancer, reported increased cardiotoxicity from trastuzumab in patients with renal dysfunction. Similar results were found in another study[82]. Notably, all the patients in this study by Russo *et al*[81] were exposed to prior chemotherapy.

Ado-trastuzumab-emtansine: It is an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a microtubule inhibitor[83]. It is used in HER2+ve metastatic breast cancer patients who progress after therapy with trastuzumab and taxanes. It has a similar distribution volume to trastuzumab but a shorter half-life (about 4 days) and is mainly cleared by the liver with minimal renal elimination[84,85]. Although there is minimal data regarding its use in chronic renal failure and HD patients, individual case reports on its safe use and lack of dosage adjustment[80,86].

The package insert recommends no dosage adjustments for CrCl ≥ 30 mL/minute. Hakroush *et al*[87] reported a case of focal segmental glomerulosclerosis after the patient started trastuzumab-emtansine (T-DM1). That improved after drug discontinuation. However, further large-scale clinical studies and post-marking analysis are needed to determine its safety in treating renal impairment. Pertuzumab is a recombinant human monoclonal antibody that targets the extracellular domain of HER2 but has a different effect than trastuzumab. It blocks the dimerization of HER2 and is known to work synergistically with trastuzumab[88].

Pertuzumab: It is used with trastuzumab in patients with locally advanced, inflammatory, early-stage, or metastatic HER2+ breast cancer. Like other monoclonal antibodies, its mechanism of elimination is minimally dependent on kidney function[89]. The NeoSphere, TRYPHAENA, and CLEOPATRA trials, which included pertuzumab use, did not demonstrate renal toxicity[90-92]. It was safely tolerated in individual case reports on patients with chronic renal failure and HD[76,93].

Margetuximab: It is a chimeric Fc-engineered monoclonal antibody that binds to HER2 with higher affinity than trastuzumab[94]. It is approved for the treatment of metastatic HER2+ breast cancer patients who have failed prior HER2-based therapies[95]. It is metabolized to smaller peptides by proteases, and no dosage adjustment is recommended for patients with mild to moderate renal impairment[94]. To our knowledge, no studies report its use in renal failure and dialysis patients.

Anti-HER2 tyrosine kinase inhibitors

Lapatinib: It is a reversible dual tyrosine kinase inhibitor that inhibits HER2 and EGFR by binding to the intracellular domain of the receptor and inhibiting cell growth[96,97]. It is approved for use in treating metastatic HER2+ breast cancer with trastuzumab or capecitabine[98]. The liver clears it with < 2% renal elimination. In a study of 11 ESRD patients with breast cancer by Pai *et al*[99], lapatinib was determined to be safe. Another case report determined its safety when combined with letrozole[26]. However, large-scale clinical trials investigating the use of lapatinib in chronic renal failure and HD patients still need to be completed.

Neratinib: It is an irreversible tyrosine kinase inhibitor of the HER1, HER2, and HER4 receptors and is approved for use in advanced HER2+ breast cancer patients[100]. Studies have also suggested its effectiveness in controlling and preventing brain metastasis in this population. Cases of acute kidney injury are likely secondary to diarrhea, which is the most common treatment-related adverse effect[101]. The package insert does not provide dose adjustment information for patients with renal function impairment, but renal function does not significantly impact neratinib pharmacokinetics. Data regarding its use in renal failure and HD patients must be included. The summary of key considerations for administering systemic therapies in breast cancer patients on hemodialysis is given in Table 1.

Table 1 Summary of key considerations for administering systemic therapies in breast cancer patients on hemodialysis

Drug	Class	Use in breast cancer	Dose adjustment in HD	Key considerations for ESRD on HD
Tamoxifen	Hormone therapy	ER-positive cancers	Yes	Monitor efficacy due to altered metabolism in HD. Reduced dose may be required
Anastrozole	Aromatase inhibitor	ER-positive cancers	Yes	Reduced clearance in HD; dose modification necessary. Monitor for reduced efficacy or increased toxicity
Letrozole	Aromatase inhibitor	ER-positive cancers	Yes	Adjust dosage for renal impairment. Monitor for adverse effects
Exemestane	Aromatase inhibitor	ER-positive cancers	Yes	Use with caution in HD. Limited data; consider alternative therapies
Cyclophosphamide	Alkylating agent	Various	Yes	Requires dose reduction. Administer post-HD due to renal excretion
Doxorubicin	Anthracycline	Various	Yes	Moderate dose reduction advised. Cardiotoxicity and clearance considerations. Administer on non-dialysis days
Paclitaxel	Taxane	Various	No	Generally safe without dose adjustment. Monitor for neuropathy and hypersensitivity reactions
Docetaxel	Taxane	Various	Yes (limited data)	Data on dialysis patients limited; likely requires dose adjustment. Monitor for neutropenia and fluid retention
Gemcitabine	Nucleoside analog	Various	No	Standard doses can be used; monitor for myelosuppression and pulmonary toxicity
Carboplatin	Platinum compound	Various	Yes	Dose adjustment based on renal function using the Calvert formula. Administer post-HD for optimal clearance
Methotrexate	Antimetabolite	Various	Yes	Contraindicated in high doses; significant dose reduction required. Avoid if possible
Trastuzumab	HER2-targeted therapy	HER2-positive cancers	No	Monitor for cardiotoxicity; minimal renal impact. Safe in ESRD on HD
Lapatinib	Tyrosine kinase inhibitor	HER2-positive cancers	Yes (limited data)	Safe in ESRD; dosage adjustments may be needed. Limited data available
Atezolizumab	Immunotherapy	Triple-negative breast cancer	Yes (limited data)	Limited data on ESRD patients. Monitor closely for immune-related adverse events
Vinorelbine	Antimitotic agent	Advanced breast cancer	Yes	Reduced initial dose recommended. Eliminated mainly through the liver, but renal adjustment necessary
Capecitabine	Prodrug to 5-FU	Various	Yes	Significant reduction in dosage needed. Monitor closely for toxicity, especially hand-foot syndrome and diarrhea
Fulvestrant	Hormone therapy	ER-positive cancers	No	No dose adjustment needed. Safe to use in ESRD patients on HD
Megestrol acetate	Progestin, antineoplastic	Cancer cachexia, appetite stimulant	No	Monitor for thrombosis risk, especially in ESRD patients
CDK 4/6 inhibitors (palbociclib, ribociclib, abemaciclib)	CDK 4/6 inhibitors	HR-positive metastatic breast cancers	Limited data	No clear dose adjustments; monitor for increased serum creatinine and potential nephroprotective effects
Cisplatin	Platinum-based chemotherapy	BRCA-1-mutated and TNBC	Yes	High risk of nephrotoxicity; use cautiously and with dose adjustments. Preferably administered immediately before HD sessions
5-FU	Antimetabolite	Various	Yes	Administer post-HD

5-FU: 5-fluorouracil; HD: Hemodialysis; ESRD: End-stage renal disease; ER: Estrogen receptor; HR: Hazard ratio; HER2: Human epidermal growth factor receptor 2; CDK: Cyclin-dependent kinase; TNBC: Triple-negative breast cancer.

IMMUNE CHECKPOINT INHIBITORS

ESRD poses significant challenges for cancer treatment due to altered drug pharmacokinetics and a heightened risk of toxicity. Immunotherapy has radically improved outcomes in patients with various malignancies, including breast cancer, but evidence in patients with ESRD is lacking[102]. There are critical knowledge gaps regarding the safety,

efficacy, and pharmacokinetics of novel immunotherapies in this population. Immunotherapy aims to stimulate the body's own immune system to identify and destroy cancer cells[55]. The major classes of immune checkpoint inhibitors include cancer vaccines and adoptive cell transfer.

In breast cancer, checkpoint inhibitors target regulatory molecules on T cells or cancer cells to enhance antitumor immunity. Commonly used checkpoint agents include cytotoxic T-lymphocyte-associated antigen 4, programmed cell death protein 1 (PD-1), and its ligand PD-L1[103]. Vaccines boost immune memory against tumor antigens, while adoptive cell transfer involves engineering and growing large numbers of antitumor lymphocytes *ex vivo* before re-infusing them[104]. However, since ESRD leads to the accumulation of immunotherapies and their metabolites, which may increase toxicity, varying renal clearance levels among different agents necessitate individual dosage adjustments. However, the data are currently minimal. General principles include avoiding nephrotoxic drugs, adjusting doses based on estimated CC, and increasing toxicity monitoring.

The PD-L1 inhibitor atezolizumab was recently approved for use in treating metastatic TBNC based on clinical trials showing efficacy[103], although data specific to the ESRD population are minimal, with less than 1% representation in pivotal studies; moreover, no dedicated ESRD-focused trials have examined atezolizumab. Preliminary case reports show potential for benefit[105]; however, appropriate dosing for patients with possible uremia-induced immune dysfunction has yet to be established, and pharmacokinetic data are lacking[106]. In addition, the risk of adverse inflammatory events provoked by checkpoint inhibition may be elevated relative to that associated with normal renal function, necessitating quantification within ESRD patients to allow risk mitigation and predictive biomarker strategies; hence, further research centered on therapeutic outcomes, side effect profiles, and ideal pharmacokinetically derived regimens for atezolizumab use in ESRD patients with advanced breast cancer is critical to guide evidence-based practice for this subset of oncology patients with high unmet needs.

Similarly, other checkpoint inhibitors overall have demonstrated survival benefits in advanced breast cancer patients, especially those with triple-negative and HER2+ subtypes[107]. However, the data available to guide usage in ESRD patients is minimal. A small study of nivolumab in advanced non-small cell lung cancer dialysis patients reported comparable efficacy to non-dialysis historical controls with increased but manageable toxicity[108]. Minimal breast cancer data exist. Overall, checkpoint inhibitors appear feasible for treating ESRD, but more extensive prospective studies are desperately needed to clarify their safe dosing and efficacy, especially in breast cancer subgroups.

Cancer vaccines and adoptive cell transfer have primarily not been studied for breast cancer in the context of ESRD. Therefore, robust clinical trials are vital to clarify the expected outcomes with these approaches. Without solid evidence, clinicians are guided by dosing recommendations based primarily on pharmacokinetic data. The NCCN guidelines advise considering reduced doses for multiple immunotherapies in severe renal dysfunction patients but do not give specific quantitative advice. The Kidney Disease Improving Global Outcomes guidelines also highlight the general need for dose reductions without any definitive recommendations[102]. Additional research is vital to establish definitive dosing and safety guidelines for prescribing different immunotherapies to ESRD patients.

PARP INHIBITORS

PARP inhibitors (*e.g.*, olaparib, talazoparib) target the DNA repair enzyme PARP, which helps repair single-strand DNA breaks. By inhibiting this, they cause double-strand breaks when DNA replicates. Cancer cells with mutations in BRCA1/2 or other homologous recombination deficiency have existing defects in the ability to repair double-strand DNA breaks. Thus PARP inhibitors are especially toxic to these cells[109].

Olaparib and talazoparib are PARP inhibitor drugs that have been approved as single-agent therapies (monotherapies) for metastatic or locally advanced HER2-negative breast cancer in patients with inherited mutations in the *BRCA* genes. Specifically, approval has been granted for cases where the *BRCA* mutation is known or suspected to be deleterious[110]. Studies have shown that impaired kidney function significantly alters the pharmacokinetics of the PARP inhibitor olaparib, resulting in increased overall exposure and peak concentrations in the body[111]. While increased adverse events were not observed, the substantially higher olaparib exposure levels associated with renal impairment could potentially lead to heightened toxicity risks, especially hematologic side effects, over time[112].

Consequently, dose reductions are recommended when administering olaparib to patients with moderate kidney dysfunction. If dose adjustments are necessary during treatment, the estimated glomerular filtration rate calculated from serum creatinine levels can sometimes overestimate the actual kidney function in these patients[113]; the aforementioned applies also to talazoparib, as significantly increased exposure combined with decreased clearance of the drug is seen in patients with impaired renal function, dose adjustments downward are recommended if treating those with moderate to severe renal impairment to mitigate likely increased toxicity[114]. Currently, there are no solid guidelines established for PARP inhibitor dosing or administration specifically adapted for ESRD patients. More research is still needed to confirm the optimal therapeutic approach to PARP inhibition in breast cancer patients with significantly reduced kidney function and ESRD patients.

CONCLUSION

The altered pharmacokinetics in these patients necessitate a tailored approach for each therapeutic agent, ensuring the best possible outcomes while minimizing adverse effects. In this literature review, we have discussed most of the drugs used in the treatment of breast cancer and whether dose adjustment needs to be made in ESRD patients on HD. However,

it is crucial to acknowledge certain limitations in our study.

In summary, the approach to breast cancer treatment in individuals with advanced renal failure undergoing HD demands a sophisticated comprehension of the pharmacokinetic changes due to renal dysfunction. Hormonal treatments such as tamoxifen and inhibitors of aromatase (anastrozole, letrozole, exemestane) require prudent management given their liver metabolism and renal excretion, with inhibitors of aromatase needing adjustments to avert toxicity. Metabolized *via* CYP3A4, fulvestrant typically does not necessitate alterations, underscoring the diversity in managing different therapies. Megestrol acetate, employed for its anticancer effects and to address cachexia in cancer, necessitates careful prescribing due to an increased risk of clotting in this demographic.

Regarding chemotherapeutic agents and therapies targeting HER2, they further exemplify the intricacies of administering breast cancer care to patients with ESRD. CTX, doxorubicin, gemcitabine, and carboplatin each require specific considerations for dosage adjustments or scheduling of dialysis procedures to maximize treatment benefits while reducing unwanted effects. On the other hand, therapies targeting HER2, such as trastuzumab, lapatinib, and pertuzumab, seem comparatively secure without significant dosage modification, although more investigation is advised to confirm these guidelines. As an emerging avenue in cancer therapy, immunotherapy demands more research to ascertain its efficacy and safety in ESRD patients. Hence, a customized strategy for each medication, informed by their pharmacokinetic profiles in advanced renal failure, is crucial for optimizing patient outcomes while minimizing potential risks in this susceptible population.

The review did not provide information about the role of radiation and surgery in breast cancer patients with HD. This omission limits the holistic understanding of treatment modalities for this patient population. A notable limitation is the scarcity of data on the role of certain drugs in breast cancer patients with HD. While we discussed most drugs, some medications lack sufficient research in this patient group, highlighting an area for future investigation. Generalizability, publication bias, methodological quality of included studies, and inclusion/exclusion criteria should be acknowledged for a more comprehensive interpretation of the review's findings.

FOOTNOTES

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