Review

Synergy of Body Composition, Exercise Oncology and Pharmacokinetics: A Narrative Review in Personalizing Paclitaxel Treatment for Breast Cancer

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Synergy of Body Composition, Exercise Oncology and Pharmacokinetics: A Narrative Review in Personalizing Paclitaxel Treatment for Breast Cancer

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Simple Summary: Paclitaxel is a widely used chemotherapy drug for breast cancer, but serious side effects, such as nerve damage and low white blood cell counts, often limit its effectiveness. Currently, chemotherapy doses are based on body surface area, but this method does not consider important individual factors like muscle and fat levels, which can affect how the drug is processed. This review explores how body composition and physical activity influence paclitaxel's effects and side effects. Regular exercise may improve treatment outcomes by supporting muscle health and reducing toxicity risks. By integrating these factors into chemotherapy dosing strategies, we can move toward a more personalized approach, ensuring that each patient receives the most effective and safest treatment. This research highlights the need for further studies to refine chemotherapy dosing, potentially leading to better treatment experiences and outcomes for breast cancer patients.

Abstract: Background/Objectives: Paclitaxel is a widely used type of chemotherapy for breast cancer, but its clinical efficacy is often hindered by dose-limiting toxicities such as chemotherapy-induced peripheral neuropathy and neutropenia. Traditional dosing based on body surface area does not account for variations in body composition, which may influence paclitaxel metabolism, toxicity, and treatment outcomes. This review explores the interplay between body composition, physical activity, and paclitaxel pharmacokinetics, emphasizing the potential for personalized dosing strategies. **Methods**: A comprehensive narrative review was conducted by analyzing literature on body composition, chemotherapy-related toxicities, pharmacokinetics, and exercise oncology. Studies examining the role of skeletal muscle mass, adipose tissue, and physical activity in modulating paclitaxel metabolism and side effects were included. **Results**: Evidence suggests that patients with low skeletal muscle mass are at a higher risk of paclitaxel-induced toxicities due to altered drug distribution and clearance. Sarcopenic obesity, characterized by low muscle and high-fat levels, further exacerbates these risks. Exercise, particularly resistance and aerobic training, has been shown to improve muscle mass, mitigate toxicities, and enhance chemotherapy tolerance. However, the

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precise mechanisms by which exercise influences paclitaxel pharmacokinetics remain underexplored **Conclusions**: Personalized chemotherapy dosing, considering body composition and physical activity, may optimize paclitaxel treatment outcomes. Future research should focus on integrating exercise interventions into oncology care and refining dosing models that account for interindividual differences in drug metabolism. These advancements could improve treatment efficacy while minimizing toxicities in breast cancer patients.

Keywords: body composition; paclitaxel; chemotherapy toxicity; pharmacokinetics; physical activity; exercise oncology

1. Introduction

Breast cancer (BC) is the most common cancer among women worldwide, accounting for 11.7% of all cancer cases, with an estimated 2.26 million new diagnoses globally in 2020 [1–3].1-3 An estimated 355,000 new cases of BC were diagnosed in the European Union (EU) in 2020, representing approximately 13.3% of all cancer cases in the region. This makes BC a significant health concern, as it also accounted for 7.3% of cancer-related deaths within the EU in 2020 [4]. Over recent decades, the survival rates and life expectancies of BC patients have significantly improved, mainly due to improvements in early detection through screening and advancements in chemotherapy and targeted therapies [4].

Depending on the stage and type of BC, treatment strategies primarily include local therapies, such as surgery with or without radiation, and systemic therapies, including chemotherapy, hormone therapy, targeted therapies, and/or immunotherapy According to major prospective clinical trials, several standard chemotherapy regimens, including anthracyclines and taxanes, are available for BC treatment [5,6]. Taxane-based regimens, such as paclitaxel (PTX), are among the most effective and commonly used systemic therapies for both early- and late-stage BC [7]. However, the toxicity associated with chemotherapy remains a significant challenge in the treatment of BC [8].

2. Paclitaxel in the Treatment of Breast Cancer

2.1. Toxicities

Paclitaxel induces cancer cell death through microtubule stabilization, leading to a mitotic arrest [9]. However, its mechanism of action can also affect healthy dividing cells, resulting in side effects. Patients with BC undergoing PTX therapy may experience a variety of toxicities, including neurological, hematological, gastrointestinal, and cardiac adverse effects, as well as hypersensitivity reactions [8,10]. The severity and presentation of these side effects can vary among patients and are often influenced by the treatment schedule and dosing protocols [10].

The toxicities associated with PTX continue to limit the effectiveness of treatment regimens based on this drug [10]. For example, while pretreatment with a standard regimen that includes a corticosteroid (such as dexamethasone) and an H1 receptor blocker can help reduce the risk of hypersensitivity reactions before PTX infusions, minor hypersensitivity reactions still occur in a significant number of patients [10,11]. Importantly, a small but critical percentage of individuals still experience life-threatening reactions [12].

The primary hematologic toxicity associated with PTX is neutropenia [13], which can be managed with the administration of granulocyte colony-stimulating factor. This leaves neurotoxicity, particularly chemotherapy-induced peripheral neuropathy (CIPN), as the main dose-limiting toxicity (DLT) [14]. CIPN, which can develop either early or late after PTX administration affects the majority of patients undergoing treatment [15]. Clinically, it is characterized by numbness and paraesthesia in a glove-and-stocking distribution, resulting from the accumulation of PTX in the dorsal root ganglia [16,17]. These DLTs can result in treatment delays, dose reductions, or even premature termination

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of therapy [18]. Additionally, they significantly impact patients' Health-Related Quality of Life (HRQoL) and functional status in both the short and long term [19].

2.2. PTX Dose Intensity

Relative dose intensity (RDI), the ratio of the actual delivered dose intensity (mg/m² per week) to the planned dose intensity for a chemotherapy regimen, is a key measure that reflects dose delays or reductions during treatment [20–22]. An RDI below 85% is considered a clinically significant reduction from the standard therapy. This decreased RDI is associated with worse outcomes, including reduced survival rates in advanced BC. This association has been demonstrated in both randomized clinical trials and retrospective observational studies [20,23,24]. Maintaining an adequate RDI is particularly important for BC patients undergoing PTX therapy, as timely administration of the planned dosage is crucial for achieving optimal prognosis. In most cancers, there is a plateau in the dose-response curve for cytotoxic chemotherapy. This means that increasing the dose towards an asymptotic threshold leads to increased toxicity without providing additional benefits to the antitumor effect [25]. Therefore, it is essential for patients undergoing chemotherapy to achieve a therapeutic response while minimizing toxicity, ensuring that their drug exposure remains at acceptable levels.

Studies have explored this dose-response relationship, specifically for PTX; however, evidence regarding PTX's therapeutic and toxic ranges is limited to certain dosing schedules [26]. Key toxicity parameters such as CIPN, have been associated with elevated maximal PTX plasma concentrations (Cmax) or prolonged exposure durations above the threshold of 0.05 μM [27–29] It is crucial to monitor and manage these toxicities to ensure an optimal RDI for patients with BC throughout their chemotherapy treatment.

2.3. Challenges in Body Surface Area Dosing of PTX

Body surface area (BSA) has long been the standard metric for determining chemotherapeutic drug dosage, as described in two reviews of 2016 [30,31]. It was initially proposed to normalize chemotherapy dosing because of the proposed relationship with other physiologic parameters, including resting energy expenditure, plasma volume, and cardiac output [32]. Various BSA formulae have been developed to simplify this process [31]. All recognised formulae are based on easily identifiable patient body variables such as height and weight, and, in some cases, age and sex [31].

However, the use of BSA as a basis for chemotherapy dosing, including PTX in BC, has long been debated due to its poor correlation with physiological parameters influencing pharmacokinetics and pharmacodynamics (PK/PD), such as differences in skeletal muscle mass (SMM), adipose tissue (AT), and metabolic activity [31]. As Miller et al. (2004) demonstrated two decades ago, BSA is proportional to blood volume, but does not accurately reflect an individual's ability to metabolize or excrete cytotoxic drugs [33]. Their study found no significant association between BSA and PTX-induced toxicities, such as leukopenia or neutropenia, suggesting that BSA is not a reliable predictor of chemotherapy toxicity .

3. Role of Body Composition and Physical Activity in Breast Cancer Treatment

3.1. Body Composition and Chemotherapy Dosingμ

Patients exhibit significant biological heterogeneity, which can affect the desired patient outcomes. Even individuals with similar or identical body weight, BSA, or body mass index (BMI) can show considerable variations in the amount and distribution of AT and lean body mass, including SMM and extracellular fluid [34]. Body composition can influence the pharmacokinetics of chemotherapy in several ways. Therefore, it has been suggested that considering body composition parameters may be more accurate than BSA for calculating the appropriate chemotherapy dosage [35].

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Changes in body composition, such as reduced SMM, decreased muscle quality and increased AT, significantly contribute to DLTs across various cancer treatments, irrespective of cancer type, age, sex, BMI, or physical function [36–39]. While there is a correlation between BMI and both SMM and AT, there is considerable variability in these measurements for any given BMI or BSA value, particularly in women with BC [34,40]. Substantial evidence supports the role of SMM and AT as predictive factors for the occurrence of DLT during chemotherapy [41–44]. Additionally, studies have shown that toxicities from anthracyclines and taxanes, such as PTX, both commonly used in BC treatment, are more closely related to SMM than to BSA [45].

In patients with metastatic BC, sarcopenia - which is defined as a reduction in SMM - has been associated with an increased risk of chemotherapy toxicities and a shorter median time to tumour progression, irrespective of overall BMI [26,45–47]. This association is particularly significant in patients with sarcopenic obesity, characterized by low SMM and high AT. Sarcopenic obesity, along with conditions like myosteatosis (fat infiltration in muscle), can lead to changes in drug distribution, metabolism and exposure. This may lead to over- (or under)dosing, increased systemic inflammation, and decreased physical resilience [37,41,48,49]. If chemotherapy dosing is based on BSA, patients with sarcopenia may receive disproportionately high doses relative to their metabolically active SMM, further increasing toxicity risks [39,50]. Similar findings have been reported in other cancer types, where patients with low SMM are at a higher risk of experiencing treatment-related toxicities [42,51–54].

Additionally, the body composition of patients with metastatic BC often differs from that of early-stage BC patients due to cancer-related fatigue, sarcopenia and/or cachexia, and treatment-related side effects such as bone demineralization (osteopenia/osteoporosis),56 reduced muscular strength [55], decreased aerobic capacity [56], and weight gain [57,58]. These observations highlight the need to better understand the role of body composition in chemotherapy tolerance among women with BC [34].

Advances in standard imaging techniques for body composition assessment, such as dual-energy X-ray absorptiometry (DXA) and single-slice Computed Tomography (CT) scan, have led to numerous studies exploring the associations between body composition and adverse outcomes in oncology [18,59,60]. Recently, artificial intelligence has been utilized to extract body composition metrics from medical images, providing new opportunities for facilitating personalized treatment approaches [61]. Given the widespread use of CT-imaging in cancer diagnosis and monitoring, body composition can be analyzed without imposing an additional burden on patients using available diagnostic images [62].

3.2. Body Composition, Paclitaxel Pharmacokinetics and Toxicities

In contrast to the numerous studies that have investigated body composition and cancer outcomes, only a limited number of trials have explored the correlation between body composition and drug PK [35]. Each drug has intrinsic properties contributing to variability in its distribution throughout the body. Hydrophilic drugs primarily distribute into lean tissue, while lipophilic drugs accumulate in the AT, affecting their volume of distribution (Vd) and elimination rate from the body [63]. Patients with sarcopenic obesity exhibit a reduced Vd for hydrophilic drugs and an increased Vd for lipophilic drugs. These alterations in drug distribution are not adequately accounted for by BSA-based dosing [39].

Several examples were identified for the chemotherapy drugs docetaxel, epirubicin and oxaliplatin. A recent study confirms that overweight and obese patients receiving adjuvant chemotherapy based on docetaxel, another taxane, have worse disease-free survival and overall survival rates, as well as a higher risk of distant metastases, compared to lean patients [63]. In contrast, no significant differences in outcomes were observed across BMI categories for patients treated with non-docetaxel–based chemotherapy. These findings may be attributed to docetaxel's lipophilic properties, leading to an increased Vd and reduced efficacy in patients with higher BMI. Although the study discusses BMI rather than body composition, the authors suggested that the risk-

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benefit ratio of using taxanes in BC should be reassessed based on patients' body composition [63]. Research conducted by Prado et al. (2011) demonstrated that variability in SMM was linked to toxicities and differences in the drug clearance of epirubicin in cancer patients, while BSA was not a reliable predictor [64]. More recent research on the PK of oxaliplatin in older adults with gastrointestinal malignancies indicated that patients with low SMM and high total AT exhibited the lowest Vd and drug clearance, the highest maximal drug concentrations, and a significantly increased risk of severe chemotherapy toxicities [65].

The hydrophobic nature of PTX leads to substantial accumulation in AT, high protein binding, and delayed clearance, contributing to its complex PK profile and toxicity risks [10,65]. A decrease in SMM is believed to influence PK by reducing the Vd, as well as affecting protein binding, drug metabolism, and clearance [35]. SMM has been reported to influence the PK of certain chemotherapeutic agents, including PTX [27,35,64,66–68]. Specifically, lower SMM, such as in patients with sarcopenia, has been associated with an increase in PTX's maximal concentration (Cmax), which likely explains the increased risk of CIPN in these patients. PK modelling simulations suggest that extending the infusion of PTX in patients with the lowest SMM may reduce CIPN while maintaining therapeutic efficacy [27]. Furthermore, not only the active compound but also that of the excipient(s) may affect drug exposure. In a study by Smorenburg et al. (2003), older adult patients with BC had up to 50% increase in PTX exposure with age [69]. This increase was attributed to a significantly altered disposition of the formulation vehicle, Cremophor EL, which was markedly decreased in the older patient group. The potential association between changes in body composition and this decrease in PTX total body clearance with age remains to be clarified [69]. Conversely, in more extensive cohort studies, older age was not identified as an independent risk factor leading to clinically relevant changes in PTX PK [70,71], suggesting that other variables, such as body composition, may be relevant. More studies are needed to examine the effects of body composition on chemotherapy PK, particularly for PTX, with adequate sample sizes and comprehensive pharmacologic endpoints [32]. Such studies will help validate preliminary findings and support the development of dosing strategies tailored to individual body compositions.

4. Role of Physical Activity and Exercise in Breast Cancer Treatment

In addition to body composition, physical activity (PA), defined as any movement resulting in energy expenditure, including leisure-time activities, and exercise, characterized as planned and structured PA aimed at improving physical capacity or physical fitness, is increasingly recognized as a crucial intervention for patients with BC during and after treatment [72,73]. Engaging in low-to-moderate levels of PA is well-known to significantly reduce mortality in patients with various malignancies [74], offering greater health benefits compared to inactivity [75]. Evidence indicates that recreational PA can lower BC mortality risk, enhance physiological and immune functions [75,76], lower stress and improve sleep disturbances and overall HRQoL [77]. Further, PA helps mitigate cancer- and treatment-related side effects, such as decreased muscular strength, weight gain, and bone demineralisation, leading to improved body composition and better clinical outcomes in patients with BC [58,72,76,78,79].

The clinical impact of exercise throughout all phases of cancer care—ranging from prevention to advanced stages and end-of-life care— is well-documented [80,81]. Therefore, physiotherapists play a pivotal role in the interdisciplinary management of cancer, contributing beyond exercise alone [82]. Exercise oncology, a relatively young discipline, emerged in the 1980s, primarily led by nurses. Early research established that exercise is feasible, safe, acceptable, and effective for individuals living with or beyond cancer [56,83–85].

In 2003, the first exercise guidelines for cancer were introduced [86]. In 2007, the Physical Activity Cancer Control framework was estabilised to delineate the different phases of cancer care [87] This framework informed the first roundtable on exercise guidelines in oncology organized by the American College of Sports Medicine in 2010 [88], with subsequent updates and expansions in 2019 [89,90]. In 2022, the American Society of Clinical Oncology (ASCO) published guidelines on

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exercise during cancer treatment [91] as well as the Dutch Royal Society for Physical Therapy (KNGF), which were later translated into English in 2023, and are now widely used in clinical practice [92].

Despite the advancements in the field of exercise oncology, two critical gaps persist. First, current guidelines predominantly emphasize rehabilitation after active medical treatment, such as chemotherapy, rather than during treatment. Second, they remain general in scope, primarily recommending PA levels similar to those for healthy populations (such as, 150 minutes of moderate-intensity exercise per week or 10,000 steps per day, as per WHO guidelines) [93]. While the long-term effects of exercise on cancer-related side effects are well-documented in these guidelines, the acute and chronic physiological responses to exercise during chemotherapy remain underexplored. Positive changes in the tumor microenvironment might be driven by accumulative effects of repeated acute exercise responses [94–96]. These acute, but short-lasting changes, that exceed the adaptive responses produced by prolonged training, might have the potential to provide immediate physiological benefits and in turn improve DLTs [96].

Addressing these gaps is essential for optimizing exercise interventions tailored to the unique needs of patients undergoing active cancer treatment. Previous studies even suggest that exercise programs can improve DLTs, like CIPN in patients undergoing taxane-, platinum-, or vinca alkaloid-based chemotherapy as concluded in the review of Wirtz et al. (2018) [78] and confirmed in the more recent review of Tanay et al. (2023) [97]. Exercise also has the potential to prevent the onset and slow the progression of CIPN, particularly in patients with BC [78,98]. This reduction in side effects may be related to multiple PK-related effects of exercise on chemotherapy that warrant further investigation. Further, exercise PK [99,100] and exercise oncology [101] are two young and promising research fields that play an important role in chemotherapy-induced DLTs.

Despite the clear benefits of exercise and PA in managing BC-related side effects, motivating women with BC to engage in regular PA remains a considerable challenge.107 Post-treatment fatigue and pain related to chemotherapy and other treatments, along with other side effects, often discourage participation in PA [102]. Various studies have demonstrated that interventions, such as cognitive behavioral strategies have added value to increase motivation and PA adherence in women with BC by implementing approaches such as behavior change techniques [103–105] and motivational interviewing [106,107]. Additionally, patients with BC often reduce their PA during therapy [108] and tend to remain physically inactive after treatment [109].

5. Body Composition, Paclitaxel Pharmacokinetics and Toxicities

Chemotherapy often leads to detrimental changes in body composition, including the loss of SMM and increased adiposity, which are associated with poor physical function and adverse treatment outcomes [110,111]. Exercise interventions have shown promising potential in positively influencing body composition in cancer patients, which may be crucial for optimizing chemotherapy dosing and improving treatment outcomes [112].

Exercise, particularly supervised aerobic and resistance exercise, during chemotherapy enhances SMM, muscle strength, and endurance, while reducing AT accumulation and improving overall body composition in patients with BC. This is supported by the meta-analysis of Li et al. (2024) [113] and other recent publications [110,111,114–123]. Resistance training has emerged as a particularly effective strategy for preserving and even restoring skeletal muscle quality [119,120]. Mijwel et al. (2019) reported that a 16-week exercise intervention during chemotherapy for BC patients significantly improved muscle strength and quality [124]. Additionally, Aires et al. (2024) emphasize the role of exercise in rebuilding skeletal muscle integrity in BC patients post-chemotherapy[114]. They suggest that targeted PA interventions could help mitigate sarcopenia and its associated risks. These functional improvements in muscle tissue may contribute to increased chemotherapy tolerance and reduced incidence of DLTs.

In the context of PTX, SMM is a critical factor influencing treatment outcomes and toxicities. Research by Wopat et al. (2024) and Poltronieri et al. (2022) reveals that lower SMM is associated with

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higher rates of DLTs, including CIPN and gastrointestinal distress [116,117]. Exercise-based interventions may mitigate these toxicities by maintaining SMM and improving metabolic function [122,123]. The review by Li et al. (2023) further demonstrates that exercise during chemotherapy not only reduces treatment-related weight gain, particularly visceral adiposity, but also enhances chemotherapy tolerance by promoting a healthier body composition profile [113].

Adipose tissue, particularly visceral and subcutaneous fat, plays a nuanced role in chemotherapy outcomes. Excess adiposity has been linked to systemic inflammation and altered drug pharmacokinetics, which exacerbates chemotherapy toxicities [118]. Exercise can attenuate these effects by reducing visceral fat and improving the visceral-to-subcutaneous adipose tissue ratio, as highlighted in studies of Poltronieri et al. (2022) and Godinho-Mota et al. (2021) [110,117]. These improvements are particularly relevant for patients undergoing PTX, where systemic inflammation is a key driver of DLTs [95,114].

Additionally, the dose and type of exercise matter. An et al. (2020) found that higher doses of resistance exercise lead to greater gains in SMM and reductions in toxicities.[128] Meanwhile Bland et al. (2022) argue for the integration of individualized exercise prescriptions tailored to patient needs and baseline PA [119]. Such targeted interventions, as evidenced by Altundag (2020), not only improve skeletal muscle index but also enhance HRQoL and reduce fatigue during chemotherapy [121]. Furthermore, Kudiarasu et al. (2023) report that combining exercise with dietary interventions yields significant improvements in both SMM and AT, supporting a multimodal approach to optimizing body composition [115].

6. Pharmacokinetics in Breast Cancer Treatment

Emerging research highlights the potential of exercise to influence drug pharmacology [32,99,125]. The review of McLaughlin et al. (2017) provides a detailed overview of the physiological changes associated with acute, subacute and chronic exercise, along with the respective drug PK variables that are affected [99].

During acute exercise, physiological changes include increased cardiac output, enhanced blood flow to active skeletal muscles, skin, digestive organs, kidneys, liver, and other tissues, as well as a decreased glomerular filtration rate [126,127]. Chronic effects are typically seen in body composition changes, such as increases in SMM and decreases in AT, along with increased serum albumin concentrations and a reduction in inflammatory cytokines [99]. The possible alteration in drug PK by exercise is likely mediated through its impact on physiological processes that regulate a drug's absorption, distribution, metabolism, and excretion [32,127,128].

First, regarding absorption, exercising may accelerate the absorption of drugs, e.g., when administered by intramuscular, subcutaneous and transdermal routes or by inhalation, due to improved blood flow [126,129]. However, the expected influence of exercise on drug absorption remains uncertain due to numerous factors, such as the physicochemical and biochemical properties of drugs, and individual anatomical and physiological variations [99].

Second, exercise can significantly impact drug distribution [126]. Acute exercise enhances splanchnic and hepatic blood flow, increasing drug delivery rates to target receptor sites and facilitating drug absorption and equilibrium between plasma and tissues [32,99]. Chronic training increases lean body mass, which is well-hydrated, while decreasing AT. On the other hand, reduced blood flow to AT and other inactive regions during exercise may slow the distribution of lipophilic drugs, such as PTX, that rely on these compartments for storage.[135] Exercise can also alter plasma protein levels. An increase in plasma protein concentration during exercise, often due to hemoconcentration from reduced plasma volume, can enhance drug binding and decrease the free, active drug fraction. For highly protein-bound drugs like PTX, this effect may further reduce the free drug concentration during or after intense PA.[104] Additionally, exercise can affect blood pH and core body temperature, leading to minimal changes in drug binding and altering the amount of free drug available in the bloodstream.[104] The clinical relevance of these changes to the final PK of the chemotherapeutic drug remains to be established.

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Third, exercise can influence drug metabolism by modulating physiological factors such as plasma volume, capillarization of skeletal and cardiac muscle, cytochrome P-450 enzyme activity, and mitochondrial density.[34] During exercise, blood flow is redirected from the liver to the muscles, which can reduce the clearance of drugs with flow-dependent hepatic metabolism, potentially influencing plasma concentrations.[135] An important chronic response to exercise is a reduction of inflammatory cytokines in cancer patients undergoing chemotherapy. A study by Schauer et al. (2021) investigated the effects of high-intensity and low-to-moderate intensity exercise on inflammatory markers in patients with BC.[100] Over six months, patients engaged in combined aerobic and resistance exercise during and after chemotherapy. The study found that, regardless of exercise intensity, levels of interleukin 6 (IL-6), IL-8, IL-10, and tumor necrosis factor alpha (TNF-α) increased post-treatment, but generally declined post-intervention.[100] Notably, high-intensity exercise resulted in a smaller increase of C-reactive protein (CRP) and TNF-α immediately post-treatment compared to low-to-moderate intensity, suggesting that high-intensity exercise may offer better protection against chemotherapy-related inflammation.[100] Whilst cytokines like IL-6 increase in the subacute period following exercise, their preliminary downregulation of CYP450 genes is eventually outweighed by a more chronic response leading to potential increases in the CYP450 microsomal content [99]. As the CYP-enzymes, CYP3A4 and CYP2C8 especially, are important for PTX metabolism, changes in their activity may influence overall metabolism [130,131].

Finally, exercise may also affect the elimination of water-soluble and renally extracted drugs and metabolites by decreasing their clearance, which, in turn, can increase their plasma concentrations,[132,135] depending on the exercise intensity.[104] Additionally, exercise can change urine pH, influencing drug ionization and affecting their reabsorption or excretion.[104] In contrast, exercise can increase the clearance of certain lipid-soluble drugs and/or metabolites by enhancing bile production and secretion, boosting biliary excretion, and reducing intestinal reabsorption, ultimately lowering plasma concentrations [99,126].

Currently, there is a limited amount of evidence regarding the impact of exercise on the bioavailability of anticancer drugs, highlighting the necessity for further research [125]. However, existing in silico models such as the physiologically based PK model published by Guo et al. (2024) offer potential for predicting of the PK behavior of chemotherapeutic drugs during exercise [127].

7. Future Directions

Future research and clinical practice in exercise oncology should prioritize integrating body composition data, PA levels and exercise into chemotherapy dosing decisions, moving beyond traditional BSA-based methods. This approach, supported by emerging evidence, promises to enhance the precision and personalization of chemotherapy, particularly for drugs with complex pharmacokinetic profiles like PTX.

In 2024, the PABTOX trial (NCT06387901) was launched at the Vrije Universiteit Brussel, Brussels, Belgium, in collaboration with the Universitair Ziekenhuis Brussel and the University of Ghent. This two-year translational research project investigates the interactions between PTX, DLTs, body composition, physical activity and various patient-specific factors. This study aims to develop a predictive PK-PD model, based on these interactions, for (DL)Ts in women with BC, treated with PTX, potentially refining chemotherapy dosing and reducing adverse effects in the future [132].

In addition to PA and low- to moderate exercise, high-intensity interval training (HIIT) during chemotherapy represents a promising area for further exploration. Limited evidence suggests that HIIT may offer superior benefits in preserving SMM, improving fitness, and reducing AT compared to traditional exercise [88,124]. Given the challenges of therapy adherence and motivation during chemotherapy, HIIT's time-efficient nature could enhance patient engagement and treatment outcomes (e.g., NCT05786014, NCT04724499, NCT05913713) Future studies should explore the feasibility and efficacy of integrating HIIT into exercise oncology programs, focusing on its impact on body composition and DLT risks in breast cancer patients.

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Moreover, the acute responses to exercise and their potential to directly influence DLTs remain underexplored. Understanding these acute responses could provide immediate physiological benefits and improve chemotherapy tolerance [94,95]. Positive changes in the tumor microenvironment driven by repeated acute exercise responses may explain observed benefits such as higher chemotherapy completion rates and improved aerobic capacity [96]. Future research should aim to elucidate these mechanisms and refine exercise prescriptions to maximize therapeutic benefits.

Additionally, integrating nutritional guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) into the care of patients with BC during chemotherapy can significantly enhance the benefits of exercise. ESPEN recommends a daily caloric intake of 25-30 kcal/kg body weight and a protein intake of 1.2-1.5 g/kg body weight to support anabolic processes and maintain SMM [133,134]. This nutritional support is crucial for optimizing body composition, as adequate protein intake is essential for muscle repair and growth, particularly when combined with resistance and aerobic exercise [133,134]. By ensuring that patients meet these nutritional targets, healthcare providers can help maximize the effectiveness of exercise interventions, reduce the incidence of DLTs, and improve overall treatment outcomes. This multimodal approach, combining tailored exercise programs with precise nutritional support, offers a comprehensive strategy to enhance HRQoL and treatment efficacy for breast cancer patients undergoing chemotherapy. There are already several examples of (ongoing) studies, combining exercise and nutritional interventions in cancer care with promising results [135,136].

8. Conclusions

This review highlights the limitations of BSA-based dosing for PTX in patients with BC and emphasizes the need to consider individual variations in body composition when optimizing treatment strategies. Differences in body composition influence the risk of toxicities, underscoring the importance of more personalized approaches to chemotherapy dosing.

Exercise and PA have emerged as modifiable factors that could positively impact treatment outcomes by improving overall physical health and enhancing chemotherapy tolerance. However, the specific mechanisms by which exercise influences the PK of chemotherapeutic drugs, including PTX, remain underexplored. Future research is critical to filling this knowledge gap and developing strategies to incorporate exercise effectively into standard treatment protocols.

By integrating body composition assessments and structured exercise (and nutritional) interventions into PTX treatment for BC, therapies can be customized for more personalized and effective outcomes as these strategies hold significant potential for reducing DLTs, improving PTX efficacy, and enhancing the HRQoL for BC patients.

As the fields of exercise oncology and personalized medicine continue to advance, exercise programs and body composition-based dosing strategies are expected to play an increasingly important role in BC care. Translational research is required to move beyond BSA-based dosing, exploring the potential value of body composition variables in PTX PK. In 2024, the PABTOX trial (Investigating Paclitaxel Toxicity in Breast Cancer: the Roles of Physical Activity and Body Composition - NCT06387901) has started patient inclusion, aiming to provide the first preliminary evidence. Future research should focus on developing and validating these approaches to improve the efficacy and tolerability of PTX treatment for BC patients.

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