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Monograph

Pharmacokinetics of cancer therapeutics and energy balance: the role of diet intake, energy expenditure, and body composition

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Abstract

Energy balance accounts for an individual's energy intake, expenditure, and storage. Each aspect of energy balance has implications for the pharmacokinetics of cancer treatments and may impact an individual's drug exposure and subsequently its tolerance and efficacy. However, the integrated effects of diet, physical activity, and body composition on drug absorption, metabolism, distribution, and excretion are not yet fully understood. This review examines the existing literature on energy balance, specifically the role of dietary intake and nutritional status, physical activity and energy expenditure, and body composition on the pharmacokinetics of cancer therapeutics. As energy balance and pharmacokinetic factors can be influenced by age-related states of metabolism and comorbidities, this review also explores the age-related impact of body composition and physiologic changes on pharmacokinetics among pediatric and older adult populations with cancer.

In 2022, there will be approximately 2 million new cancer cases and more than half a million cancer deaths in the United States alone (1). Although enormous strides have been made in cancer treatments over the last several decades, variability in treatment tolerability, particularly for chemotherapy, remains an important issue in clinical practice. Given the narrow therapeutic range of many cancer therapies, understanding what impacts individual patient variation in drug exposure and treatment tolerability is critical to optimizing care. Understanding how medications move throughout the body, including their absorption, metabolism, distribution, and excretion, known as pharmacokinetics (PK), is paramount to optimizing treatment decisions and dosing considerations (2).

One crucial factor that may contribute to the PK of cancer therapies is energy balance, which consists of energy (dietary) intake, energy expenditure, and energy storage. There is growing evidence that specific aspects of energy balance, such as healthy dietary intake and moderate to high levels of physical activity, can reduce the risk of morbidity and mortality after a cancer diagnosis. However, how energy intake and expenditure per se impact chemotherapy PK and treatment tolerability is less understood. Furthermore, the role of body composition as an index of energy storage in predicting cancer outcomes is of increasing interest within oncology (3,4). Low muscle mass and strength, commonly known as sarcopenia, are strongly associated with survival and chemotherapy toxicity (5,6). Similarly, sarcopenic obesity (eg, low muscle and excess fat mass) and myosteatosis (fat infiltration in muscle) are risk factors for increased toxicities and adverse outcomes (7,8). How these factors precisely influence PK and chemotherapy toxicities remains unclear.

The overall objective of this review is to examine the existing literature on the impact of energy balance on the PK of cancer

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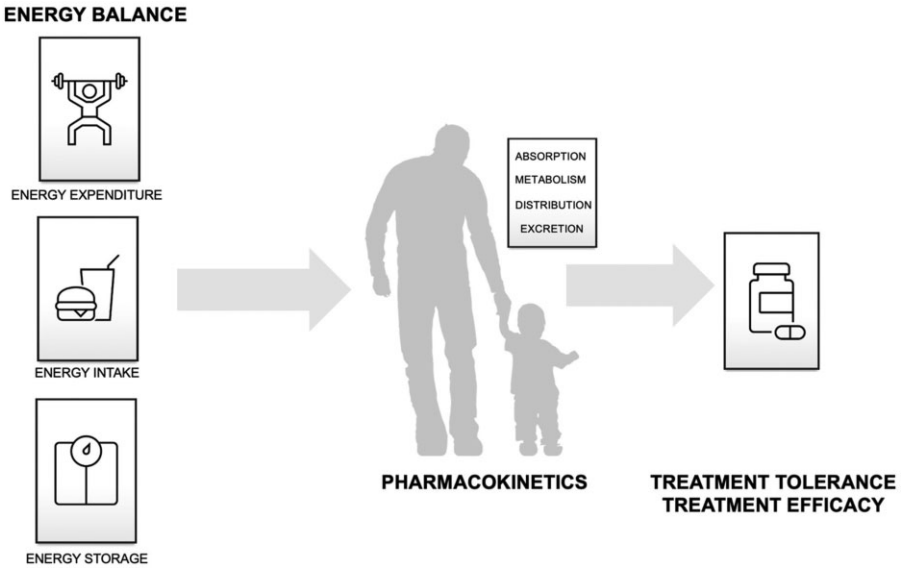

Figure 1. Impact of energy balance on pharmacokinetics of cancer therapeutics.

therapeutics, particularly chemotherapy (Figure 1). More specifically, we examine the role of dietary intake, nutritional status, energy expenditure, and body composition in influencing cancer treatment PK. In addition, we explore the existing evidence of energy balance parameters impacting PK related to special populations, including pediatric and older adult populations with cancer. For this review, we focused on energy balance and PK given our interest in how the body and energy balance may affect cancer therapies. Pharmacodynamics (PD) is a related topic that examines how a drug affects the body and its intended biologic effect, but it is not a focus of this review.

Energy intake: diet and nutrition

Acute dietary intake

Acute (recent) dietary intake can substantially impact the PK of some oral drugs, including many cancer therapeutics (9). Compared with fasted conditions, acute dietary intake can alter gastric acidity, increase splanchnic and hepatic blood flow, stimulate bile production and release, and influence gastrointestinal transit times (9,10). Collectively, these factors can impact absorption, distribution, metabolism, and excretion—and, hence, the PK—of oral drugs (11,12). Earlier work has demonstrated that half of all chemotherapeutics approved by the US Food and Drug Administration (FDA) between 1971 to 2013 required consumption either in fasted or fed conditions, with the other half not requiring consideration of prior food (13).

Because many drugs interact with food, food-effect bioavailability studies are a cornerstone for assessing the efficacy and tolerance of orally administered drugs and for obtaining FDA or European Medicine Agency approval for use (12,14). Currently, the FDA and European Medicine Agency recommend assessing oral drug bioavailability after consuming a meal high in energy and fat (800-1000 kcal; 500-600 kcal from fat). If a food–drug interaction is present, further testing with a meal containing a moderate amount of energy and fat (400-500 kcal; approximately 150 kcal from fat) may be warranted (14); however, there is no guidance regarding low-fat meals (15).

Guidelines on diet–drug interaction testing and directions for use are largely adequate for ensuring safe and effective chemotherapy dosing. However, there are specific foods or acute dietary intake patterns that may impact the PK of chemotherapeutics that are not identified in pre-approval testing. In one example of a randomized crossover trial, 28 patients with non-small cell lung cancer received concomitant treatment with erlotinib (targeted therapy) with or without esomeprazole (proton pump inhibitor) and with either 250 mL of cola or water for 7 days (16). In patients taking proton pump inhibitors, the mean area under the plasma concentration time curve (area under the curve [AUC]) was 39% higher, and the maximum serum concentration was 42% higher after consumption of the cola compared with water, likely because cola alters stomach acidity and thus the solubility and availability and PK of erlotinib (16). In another example, low-dose (250 mg) abiraterone acetate (androgen synthesis inhibitor) consumed with a low-fat meal was noninferior to the standard dose (1000 mg) consumed in fasting conditions among 36 patients with metastatic castration-resistant prostate cancer (17). Given the diversity of dietary intake in free-living conditions, continued exploration of acute diet–PK interactions could have substantial ramifications for patients, prescribers, and payers—especially for drugs with a narrow therapeutic range in which acute dietary intake could precipitate underdosing or toxicity (18). Notably, PK-informed recommendations regarding acute dietary intake often require behavior changes, which may not be followed by all patients. For example, 41% of individuals with cancer did not consider their last meal before taking oral chemotherapy, and only 20% correctly identified food–drug interactions from their chemotherapy (19). Recommendations for acute dietary intake also assume patients have adequate resources and knowledge to make appropriate changes (eg, the meaning of low fat or fasting). However, there is a lack of dissemination of trustworthy nutrition information for people with cancer (20). Cultural and religious practices such as Ramadan fasting may also impact dietary intake and thus PK of the chemotherapeutics used (21,22). Therefore, delineating diet–PK interactions may help refine behavioral approaches for enhancing cancer treatment efficacy.

Moderate- and long-term dietary intake

Whereas acute dietary intake is an important consideration in PK, there is limited knowledge on how moderate- or long-term

dietary habits over days, weeks, or months may affect cancer therapeutics PK. Data from oral drugs used for conditions other than cancer suggest that some dietary patterns elicit changes in whole-body metabolism that impact the absorption, distribution, metabolism, and excretion of drugs. For example, changes in macronutrient distribution may alter drug-protein binding capacities, cholesterol levels, or bile acid turnover, which in turn impact serum concentrations of antiepileptic drugs (23,24). Even 3 days of a high-fat diet can increase the exposure of midazolam and omeprazole in healthy individuals, potentially through alterations in the cytochrome P450 enzyme system (25). Similarly, a 10-day high-protein, low-carbohydrate diet can increase the clearance of propranolol and theophylline in healthy individuals (26).

In the context of cancer, most studies of moderate- or long-term diet–PK interactions have been conducted in animals and generally report that protein or energy intake restriction results in lower clearance or increased absorption of common chemotherapeutic and other cancer agents (ie, 5-fluorouracil, methotrexate, anthracycline, vinca alkaloids, etoposide, erlotinib) (27). Animal studies can clarify the mechanistic basis for PK in response to dietary patterns in controlled settings. However, human applicability may be limited because animal studies often use extreme modulations in protein or energy intake implausible in humans. Many studies of chemotherapy agents in animals have administered diets devoid of protein or only approximately 3% of energy intake from protein, whereas protein malnutrition has been associated with altered clearance or toxicity profiles of chemotherapeutic agents (28,29).

Understanding dietary intake–PK relationships in humans is also vital, considering increased public and research interest in intermittent fasting, fasting-mimicking diets, or time-restricted eating practices to improve response to certain chemotherapies (30,31). It has been suggested that fasting may reduce the amount and severity of toxicities while preserving antitumor effects treatment (32); however, whether this occurs through changes in PK is largely unknown. In one published randomized crossover trial (and the only one of its kind to our knowledge), patients with solid tumors and liver metastases underwent 30% energy intake restriction and 70% protein restriction for 5 days before irinotecan administration vs their regular diet (33). Calorie and protein restriction resulted in higher 24-hour plasma AUC of irinotecan and its active metabolite SN-38 compared with regular diets, with no difference in toxicities. Notably, protein and calorie restriction resulted in weight loss over the first chemotherapy cycle, although most patients regained their initial weight 2 weeks after the diet period. As previously reviewed, fasting may be a potentially feasible and promising method of maximizing treatment efficacy; however, current evidence in humans is limited and primarily focuses on extended fasting protocols (34) (refs). Short-term fasting or intermittent fasting may be particularly relevant given the promise of chronomodulated chemotherapy in which treatment administration is based on circadian rhythms. As highlighted by a recent systematic review, this approach may reduce toxicity and preserve the efficacy of many common chemotherapy regimens (35). Interestingly, although many chronomodulated chemotherapy regimens included in the review scheduled dosing initiation or peak in the early morning hours, none considered recent dietary intake, dietary patterns, or fasting. Thus, the relative contribution of biological variation based on circadian rhythms or behavioral factors such as the timing of dietary intake on treatment outcomes is unclear. Given the potential positive effects of fasting but adverse effects of weight loss in some patients with cancer (36,37), more mechanistic PK research is needed to identify which patient populations may benefit from specific and novel dietary intake patterns.

Nutritional status

The National Cancer Institute defines nutritional status as "the state of a person's health in terms of the nutrients in his or her diet." It considers a more comprehensive view of health by encompassing patient characteristics such as anthropometric data (including body composition), biochemical parameters, clinical assessment, and dietary intake.

There are several methods to determine nutritional status, but the Scored Patient-Generated Subjective Global Assessment (PG-SGA) is one of the most commonly used tools in research and clinical oncology settings (38,39). This questionnaire is a 4-in-1 clinical instrument for nutritional screening, assessment, intervention triage, and monitoring. Several previous studies have found scores from the full and short forms of the PG-SGA predict important clinical outcomes such as length of hospital stays, quality of life, postoperative complications, medical costs, and survival (40). There is also evidence that malnutrition, as assessed by the PG-SGA, is related to a higher prevalence of treatment toxicities and dose reductions and poorer treatment response rates and disease control (41-43).

The predictive ability of the PG-SGA is likely because it measures global risk for malnutrition rather than nutritional deficit alone (40). However, it is not clear if associations between PG-SGA score and treatment outcomes are mainly due to alterations in physical function and body composition or if nutritional status as assessed by the PG-SGA directly relates to PK. As an illustrative example, we assessed PG-SGA scores and oxaliplatin PK among 25 older adults with gastrointestinal cancers [NCT03998202 (44)]. As shown in Figure 2, PG-SGA total score was negatively correlated with the volume of distribution and clearance of oxaliplatin, indicating that worse nutritional status was associated with lower values of these 2 PK parameters (and higher exposure to oxaliplatin). After adjusting for body surface areas via partial correlation, the relationship between PG-SGA and clearance remained statistically significant (Spearman rho = −0.419; $P = .047$), with a trend toward statistical significance between the PG-SGA and volume of distribution (Spearman rho = −0.397; $P = .061$). Given this exploratory data, altered PK may contribute to worse clinical outcomes observed in patients with poor nutritional status. However, the utility of using more general and accessible measures of long-term and current nutritional status—such as the PG-SGA—to predict PK-related parameters is unknown and needs to be established in future studies.

Energy expenditure: focus on exercise

Total daily energy expenditure consists of resting energy expenditure (energy used to maintain bodily function; the largest component of total daily energy expenditure), physical activity energy expenditure (energy used to move the body), and the thermic effect of food (energy used to digest and assimilate consumed nutrients). In patients with advanced cancer, tumor burden and associated systemic inflammation may increase resting energy expenditure (45), but this may not be reflected in free-living total energy expenditure in patients with primarily earlier-stage cancer (46). Although preliminary evidence suggests that resting energy expenditure may relate to cancer treatment outcomes (47), no study to date has assessed energy expenditure and PK specifically. Similarly, there is limited data on the thermic

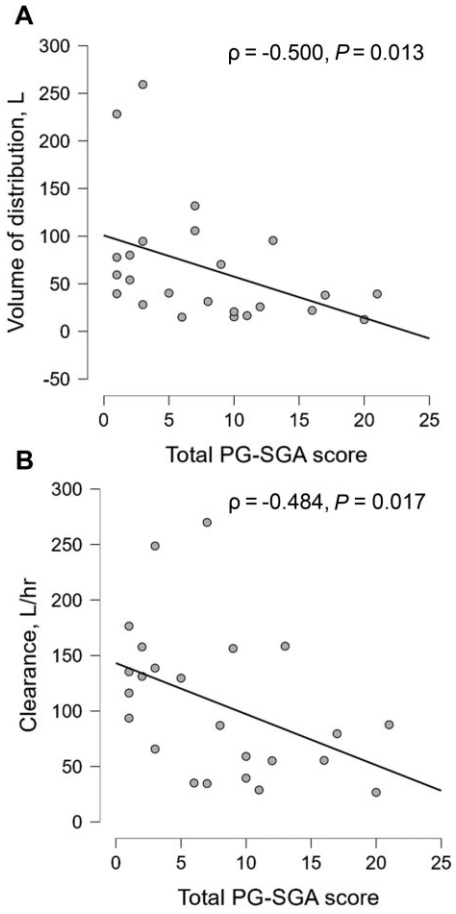

Figure 2. Relationship between total short-form Patient-generated Subjective Global Assessment (PG-SGA) score and volume of distribution **(A)** and clearance **(B)** of oxaliplatin. Participants were n = 25 patients with gastrointestinal cancer (n = 12 colon, n = 7 pancreatic, n = 3 esophageal, n = 1 appendix, n = 1 rectal), with a median age of 69 years and predominantly male (68%).

effect of food in cancer in general (48–50), and none that investigates this energy expenditure component in relation to PK. As such, we will focus our discussion on energy expenditure–PK relationships on physical activity energy expenditure.

Physical activity energy expenditure is broadly categorized as the energy used to perform structured exercise or nonexercise activities (eg, movement from occupations, sitting, standing, ambulatory activities). Exercise is a critical consideration in the PK of many drugs because it acutely increases cardiac output, which enhances blood flow to metabolically active tissues and organs (eg, skeletal muscle, heart, lungs). Greater blood flow affects PK activity by increasing the amount of drug reaching appropriate receptor sites. Hence, as muscle blood flow increases with exercise, drug absorption and equilibrium between plasma and organ and/or tissues increases. When exercise ceases, constriction of arterioles in muscles and decreased splanchnic blood flow decrease drug re-entry in the circulatory system. Regular exercise can enhance the metabolic efficiency and activity of drugs, perhaps through physiological changes in cytochrome P-450 isozyme levels, plasma volume, plasma proteins (eg, serum albumin), body composition, capillarization of heart and skeletal muscle, and tissue mitochondrial density. Drug-specific factors such as membrane permeability and pH and whether a drug is flow limited (weakly bound, highly extracted) or capacity limited (strongly bound, poorly extracted) may impact exercise–PK relationships. However, the limited data in this area preclude definitive estimations of drug distribution by exercise.

Although much can be gleaned from the effect of exercise and the PK of drugs in the realm of cardiovascular disease and diabetes (eg, exercise increases the rate of insulin absorption in patients receiving basal dosing) (51,52), no studies to date have examined the role of exercise on the PK of cancer drugs. This research gap was recently highlighted by an attempt to perform a systematic review on this topic by Curnier (53); following an extensive literature search, the authors concluded there is a lack of data examining the role of exercise on the PK of cancer drugs. Theoretically, exercise influences on PK mentioned above may subsequently influence chemotherapy efficacy. Several preclinical models have concluded that exercise can affect cancer treatment efficacy by slowing tumor growth and progression (54–56). These outcomes have been attributed to regulating intratumoral vascular maturity, perfusion, hypoxia, and tumor cell metabolism (57), suggesting improved drug delivery and a positive treatment effect.

Exercise increases the efficiency of oxygen utilization by muscle and thus increases aerobic capacity. Aerobic capacity, or VO2 max, is the maximum volume of oxygen the body can utilize in a given amount of time. By increasing aerobic capacity and producing greater uptake and delivery of oxygen during exercise, the typically hypoxic tumor microenvironment may be reversed (58). One mechanism for this is the effect of exercise on tumor vasculature through its remodeling of unorganized vessel sprouts to more organized and elongated vessels that allow for increased oxygen delivery to the tumor, as well as increased drug delivery and distribution (59). Studies like this have laid the groundwork to support safety and feasibility studies of exercise during chemotherapy infusion (60); however, alterations in cancer drug metabolism have yet to be studied.

Clinical studies have also demonstrated that exercise improves cancer treatment–related side effects, which may lead to improved treatment completion rates (61). This decrease in side effects may be related to multiple PK-related effects of exercise on chemotherapy that have yet to be studied. For example, exercise may decrease unwanted side effects of chemotherapy by increasing the rate of excretion or changing the distribution of the drug. It may stand to reason that an increased excretion rate may negatively impact chemotherapy efficacy, yet preclinical models have shown the opposite through a synergistic effect with chemotherapy (56). In multiple mouse models of sarcoma tumors, when exercise was combined with chemotherapy, a greater reduction in tumor burden was seen when compared with chemotherapy alone, thus synergistically improving chemotherapy efficacy (56,59). Despite preliminary evidence suggesting exercise improves treatment adherence and rate of completion, future clinical studies on the effect of exercise on the bioavailability of cancer drugs are necessary to understand whether these changes impact desired therapeutic outcomes.

Regardless of PK, the latest American Society of Clinical Oncology guidelines on exercise, diet, and weight management during cancer treatment strongly recommend aerobic and resistance exercise during active cancer treatment to mitigate side effects (62). Although clinical evidence currently does not sufficiently support exercise to improve cancer control or improvement in relative dose intensity of therapy regimens, the physical and psychosocial benefits outweigh the harms. Benefits may include reduced fatigue; preserved cardiorespiratory fitness and physical function and strength; and improved quality of life, anxiety, and depression with a low risk of adverse events. Further

research is needed to understand if altered PK that maximizes chemotherapy treatment is also a benefit of exercise.

Body composition

With the growing ability to utilize routine computed tomography (63) for body composition analyses, many studies have examined the link between body composition and adverse outcomes in oncology (4). The first meta-analysis of sarcopenia demonstrated a 44% increased risk of death in patients with cancer and low skeletal muscle mass, regardless of cancer type or disease stage (5). Similarly, low skeletal muscle mass is predictive of 4.08 higher odds of severe chemotherapy toxicity (95% confidence interval [CI] = 2.48 to 6.70) and 2.24 higher odds of dose-limited chemotherapy toxicity (95% CI = 1.28 to 3.92) (64). What underpins these associations remains unclear and is a focus of ongoing research. In 2016 Prior et al. (65) found that sarcopenia is associated with lower exercise capacity, which could result in limiting diffusion of substrates, oxygen, hormones, and nutrients necessary to counter metabolic-related chemotherapy toxicities. Many initially hypothesized that low skeletal muscle mass was synonymous with reduced performance status, physical function deficits, and increased frailty; however, these deficits are poorly associated with skeletal muscle mass (66,67). An alternative hypothesis increasingly gaining traction to explain the increased chemotherapy toxicities is related to altered PK. The dosing of the vast majority of cytotoxic chemotherapeutics is based on body surface area (BSA). BSA was initially proposed to normalize chemotherapy dosing because of the proposed relationship of BSA with other physiologic parameters, including resting energy expenditure, plasma volume, and cardiac output (68). Although several studies have shown that BSA only modestly reduces interpatient drug variability (69,70), it remains commonplace in oncology practice. BSA-based dosing relies solely on height and weight and does not consider variations in body composition (71). A wide distribution of lean body mass and adipose is observed for any given BSA and may affect altered chemotherapy volume of distribution, metabolism, and clearance of hydrophilic and lipophilic drugs from the systemic circulation thereby reducing treatment efficacy and excess toxicity.

In contrast to the many studies examining body composition and cancer outcomes, only a few studies have examined body composition and drug PK (72). In one of the first studies in 2011 by Prado et al. (73), lean body mass was highly variable, associated with toxicities, and explained 33% of the variance in the clearance of epirubicin in patients with breast cancer. Importantly, BSA was not predictive of lean body mass or associated with epirubicin clearance (73). In 2012 Mir et al. (74) found similar results with sorafenib in patients with advanced hepatocellular carcinoma. Patients with sarcopenia experienced significantly more dose-limiting toxicities (82% vs 31%; $P = .005$) and had statistically significantly higher median sorafenib plasma AUC (102.4 mg/l.h vs 53.7 mg/l.h; $P = .013$). A more recent study examined oxaliplatin PK in 26 older adults with gastrointestinal malignancies and showed the body composition phenotype of low lean body mass and high total adipose tissue had the lowest volume of distribution, lowest clearance, highest max drug concentrations, and a 45% increased risk of severe grade 3-5 chemotherapy toxicities (2). Population PK models of oxaliplatin demonstrated that total adipose tissue, lean body mass, and serum albumin explained 14%, 11%, and 17%, respectively, of oxaliplatin variability beyond BSA.

However, not all studies have observed similar findings. The results for 5-fluorouracil have been mixed, with one study finding no association between skeletal muscle mass and first-cycle AUC. In contrast, another study found improvements in the 5-fluorouracil clearance model fit with the addition of the skeletal muscle index (75,76). Another study of capecitabine, an oral prodrug of 5-fluorouracil, found no association between skeletal muscle mass and PK parameters (77). These contrasting findings are not wholly unexpected, as the association between chemotherapy PK and body composition will largely be drug specific and depends greatly on the hydrophilic or hydrophobic nature of the specific compound and how it distributes within the body.

Special populations

Pediatrics

Because of major advances in cancer-directed therapies over the last several decades, long-term survival for childhood cancer is now more than 80% (78). However, owing to their exposure to antineoplastic agents, childhood cancer survivors experience a significantly greater burden of chronic health conditions at a far younger age when compared with the general population (63). Gaining a better understanding of energy balance and chemotherapeutic PK in children as they age into adolescence and young adulthood may enable a more precise mechanism of dosing antitumor agents in the pediatric population, thereby potentially mitigating some of the short- and long-term adverse effects in this at-risk group (79).

To our knowledge, no study has assessed dietary intake and exercise on PK parameters in pediatrics per se. However, some have investigated the "energy storage" aspect of energy balance by characterizing body weight or composition on PK (79). Though the poor association between body mass index (BMI) and body composition is well recognized, and it is understood that traditional methods of dosing by BSA do not accurately predict chemotherapy PK, pediatric clinical studies involving chemotherapy PK have primarily focused on the effects of BMI (80). Results of these investigations have been mixed; however, publications on conventional chemotherapy agents including doxorubicin, mercaptopurine, busulfan, and more recently, high-dose methotrexate and asparaginase demonstrate that adiposity does alter cytotoxic drug activity among children with cancer (81–84).

Browning and colleagues (81) demonstrated that weight-based dosing of busulfan among children with high BMI resulted in higher than expected drug concentrations. Conversely, Zuccaro et al. (82) showed that dosing of 6-mercaptopurine based on BSA resulted in underdosing among overweight children. Thompson et al. (83) showed that pediatric oncology patients with more than 30% body fat exhibited disturbed clearance of the doxorubicin metabolite, doxorubicinol. Similarly, Orgel and colleagues (84) showed that, among acute lymphocytic leukemia patients, obesity was associated with delayed clearance of high-dose methotrexate and increased risk of asparaginase-associated toxicity. Human studies align with some preclinical studies, showing that vincristine PK is altered in obese vs nonobese leukemia mouse models, leading to decreased overall drug exposure among obese mice (85). Changes in PK can have serious implications for treatment efficacy in pediatrics; for example, a retrospective study by Bhandari et al. (86) demonstrated that pediatric patients with solid tumors treated with cisplatin-containing regimens with obesity at diagnosis had a threefold greater risk for developing severe treatment-related toxicity.

The impact of body composition on PK extends beyond traditional chemotherapies. Crizotinib, a potent oral tyrosine kinase inhibitor, has increasingly been studied in pediatric solid tumors and brain tumors. In one study, overweight and/or obese status significantly influenced crizotinib PK, resulting in a clinically relevant impact (>20%) on drug exposure (87). Additionally, in a study of pediatric patients with osteosarcoma, body composition was a key determinant of exposure to bevacizumab, a humanized monoclonal antibody that inhibits vascular endothelial growth factor, and BMI was statistically significantly correlated to bodyweight normalized clearance and volume of distribution, similar to studies in adult patients (88). Bevacizumab dosing adjusted for body composition in children may minimize PK variability and reduce the likelihood of major wound-healing complications. Evaluating the impact of energy balance and PK of targeted therapies is needed in the pediatric population, and future studies should be conducted as these agents become increasingly used in the pediatric cancer population.

Older adults

Most cancer diagnoses occur in adults aged older than 65 years, and given changing demographics, it is estimated that approximately 70% of all cancer diagnoses will be among older adults by 2030 (89). The management of older adults is made uniquely challenging because of large variability in treatment tolerability related to comorbid conditions and aging-related impairments that are not adequately explained by chronologic age alone (90,91). Generally, dietary intake and nutritional status change in late life. Specifically, aging may be associated with loss of appetite, taste and smell alterations, poorer oral health, reduced ability to swallow, mobility constraints, and socioeconomic barriers that contribute to poor quality and quantity of dietary intake (92). These factors collectively place older adults at high risk for poor nutritional status; in fact, 8.5% of community-dwelling older adults and 28.0% of older adults in the hospital are at risk of malnutrition (93). Cross-sectional studies indicate that total energy expenditure begins to decline around ages 50-60 years, likely driven by decreased resting and physical activity energy expenditure (94). In terms of energy storage, older adults are at increased risk for and have a higher prevalence of sarcopenia and myosteatosis, which may partly explain differences in treatment tolerability (95,96). For example, in a recent large study of adults with colorectal cancer, only 26.8% of adults aged younger than 60 years were identified as sarcopenic, whereas 58.3% of those aged older than 70 years were sarcopenic (97). Older adults diagnosed with cancer and undergoing cancer treatment also have evidence of an accelerated loss of lean mass compared with noncancer populations (98). Furthermore, the aging process is accompanied by aging-related declines in physiology and organ function, such as reduced liver size and glomerular filtration rate, that impact PK through changes in absorption, metabolism, drug distribution, and excretion (3).

Although older adults represent most of the cancer population, older adults are frequently underrepresented in clinical trials, and few studies have specifically examined this vulnerable population (99). Most studies to date have focused on mixed populations of adults, and we were unable to identify any that specifically examined the impact of energy balance on PK considerations in older adults with cancer. However, a recent perspective on chemotherapy dosing considerations in older adults identified 7 studies examining age-related PK changes among older adult populations (3). In one study by Lichtman et al. (100), paclitaxel given every 3 weeks examined age-related changes in PK and demonstrated a statistically significant association between age and rise in AUC and decline in clearance. For the growing number of vulnerable older adults diagnosed with cancer, treatment decisions are complicated by many factors, and there are many age-related considerations that may impact cancer therapeutic dosing, potentially including energy balance, but this has yet to be fully elucidated.

Future Directions

Understanding the multiple facets of energy balance and how they may impact PK of chemotherapeutics is critical to optimizing care across the cancer population. Yet, the literature is sparse, with many research gaps. More research is needed to identify which patient populations may benefit from acute dietary intake and novel nutritional strategies. For example, consideration of PK in response to various fasting protocols would help clarify the safety and therapeutic benefit of this popular dietary pattern. Further understanding of the relationship between general nutritional status and PK may also help develop and refine targeted interventions to maximize treatment response. Although the physical and psychosocial benefits outweigh the potential harms of exercise during cancer treatment, understanding the impact exercise has on PK, such as drug absorption, drug distribution, and drug metabolism, as well as cancer outcomes, is warranted. In addition, more studies examining the impact of body composition (skeletal muscle, adipose tissue, and other organs) on chemotherapeutic PK that are adequately powered and with sufficient pharmacologic endpoints are necessary to confirm preliminary findings and ultimately develop body composition–informed dosing strategies. Next, studies should focus not only on adults but also on important populations frequently underrepresented in clinical trials, particularly pediatric and older adult populations, as these are unique groups warranting specific consideration. Lastly, cotranslational approaches bridging preclinical and clinical investigations are needed to better leverage the notable gaps in both research approaches.

Data availability

No new data were generated or analyzed in support of this research.

Author contributions

Sarah Purcell, PhD (Conceptualization; Data curation; Writing—original draft; Writing—review & editing), Dieuwertje Kok, PhD (Conceptualization; Data curation; Writing—original draft; Writing—review & editing), Tyler Ketterl, PhD (Conceptualization; Data curation; Writing—original draft; Writing—review & editing), Miriam Garcia, MD (Conceptualization; Data curation; Writing—original draft; Writing—review & editing), Lenat Joffe, MD (Conceptualization; Data curation; Writing—original draft; Writing—review & editing), Justin Brown, PhD (Conceptualization; Data curation; Writing—original draft; Writing—review & editing), Christina M. Dieli-Conwright, PhD, MPH (Conceptualization; Data curation; Writing—original draft; Writing—review & editing), and Grant Williams, MD (Conceptualization; Data curation; Writing—original draft; Writing—review & editing).

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Conflicts of interest

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