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REVIEW

Antineoplastic dosing in overweight and obese cancer patients: an Associazione Italiana Oncologia Medica (AIOM)/Associazione Medici Diabetologi (AMD)/Società Italiana Endocrinologia (SIE)/Società Italiana Farmacologia (SIF) multidisciplinary consensus position paper

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Most anticancer molecules are administered in body-size-based dosing schedules, bringing up unsolved issues regarding pharmacokinetic data in heavy patients. The worldwide spread of obesity has not been matched by improved methods and strategies for tailored drug dosage in this population. The weight or body surface area (BSA)-based approaches may fail to fully reflect the complexity of the anthropometric features besides obesity in cancer patients suffering from sarcopenia. Likewise, there is a lack of pharmacokinetic data on obese patients for the majority of chemotherapeutic agents as well as for new target drugs and immunotherapy. Therefore, although the available findings point to the role of dose intensity in cancer treatment, and support full weight-based dosing, empirical dose capping often occurs in clinical practice in order to avoid toxicity. Thus a panel of experts of the Associazione Italiana Oncologia Medica (AIOM), Associazione Medici Diabetologi (AMD), Società Italiana Endocrinologia (SIE), and Società Italiana Farmacologia (SIF), provides here a consensus statement for appropriate cytotoxic chemotherapy and new biological cancer drug dosing in obese patients.

Key words: obesity, BSA, cancer drug dosing, chemotherapy dose, pharmacokinetic parameters

INTRODUCTION

A direct link between excess body weight and both increased cancer risk and worse cancer outcomes has been seen to be rising globally over recent decades.[1-4] Obesity-related cancer accounts for 3.9% of all cancers worldwide, reaching between 7% and 8% in some high-income countries.[3] Current evidence indicates that a 5 kg/m^2 increase in body mass index (BMI) is associated with higher risk for several cancers, such as esophageal adenocarcinoma and endometrial, renal, colon and postmenopausal breast cancers.[4-6] The International Agency for Research on Cancer has reviewed studies on the association between the amount of body fat and risk for 13 different cancer sites. The relative risk associated with a BMI $\geq$40 was up to 4.8 for esophageal adenocarcinoma and 7.1 for endometrial cancer, while physiological levels of adipose mass were associated with lower risk for most cancers.[3]

Poorer outcomes and the higher cancer mortality rates among obese patients are multifactorial, while it is often

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the case that empirically lower than full-weight-based chemotherapy dosage could be a potential explanation. Indeed, the clinical practice of dose capping to limit toxicities occurs in up to 40% of heavy cancer patients in the absence of outstanding clinical evidence.[7] In 2012, therefore, the American Society of Clinical Oncology (ASCO) released clinical practice guidelines for clinicians to adjust chemotherapy dosage calculations to take account of actual body weight.[8] No recommendations have however been provided for new target drugs and immunotherapy. There is moreover a lack of prospective randomized controlled clinical trials (RCTs) exploring the optimal dose of anticancer treatment in patients with excess body weight, who are also frequently under-represented in studies on novel anticancer drugs.

Anticancer agent doses are personalized according to the patient's weight or body surface area (BSA).[9] Less common methods for determining dosing for adult cancer patients include 'flat-fixed' dosing[10] and 'dose banding'[11] which help to avoid potential calculation errors. It is well known that anthropometric changes in obese individuals, as regards body proportions of water, fat and muscle mass, are accompanied by variations in district-specific blood flow, alterations of liver and renal functions and chronic, low-grade inflammatory state.[12] All of these critical factors impact on pharmacokinetic (PK) parameters as well as pharmacodynamic (PD) endpoints of a given drug.[13]

Overall, the complex PK changes observed in obese individuals may, at least partially, explain why several limitations are observed when BMI and BSA are used to adapt treatments to overweight or obese patients.[14] The assumption behind both scenarios is that the PK and PD of each drug increases in proportion to weight or BSA. This is however often not the case since BMI and BSA are not informative on body composition as they fail to distinguish between fat and lean tissue mass.

The poor reliability of currently employed dose adjustment strategies is a critical clinical issue for anticancer drugs whose narrow therapeutic index may result in drug overexposure (weight-based approach) or underexposure (BSA-based approach) in obese patients. This may mean an increased risk of toxicity on the one hand or risk of underdosing on the other.[8,15] The question arises therefore of whether the adoption of personalized drug dosage in overweight/obese patients is really necessary.[16]

The Associazione Italiana Oncologia Medica (AIOM), the Associazione Medici Diabetologi (AMD), the Società Italiana Endocrinologia (SIE) and the Società Italiana Farmacologia (SIF) have gathered together here a panel of experts to review the current evidence on this topic and formulate a consensus for recommendations addressing dosages for cytotoxic chemotherapy, novel immunotherapies and targeted agents in overweight and obese adults.

MATERIALS AND METHODS

A web-based search of Medline/PubMed library data published for all relevant studies up to March 2021 was carried out using the following keywords: 'obesity' OR 'obese' OR 'overweight' OR 'body weight' AND 'cancer' OR 'tumour' OR 'neoplasms' AND 'dose' OR 'dosing' AND 'chemotherapy' OR 'drug therapy' OR 'targeted therapy' OR 'target therapy' OR 'immunotherapy' OR 'immune checkpoint inhibitors'. The identified reports were independently screened by two investigators (A.A. and N.S.). Only papers written in English were included. Each paper was retrieved and its references were reviewed to identify additional studies. Most of the studies included in this consensus paper refer to retrospective analyses of RCTs and observational studies comparing full-weight and non-full-weight dose for antitumor therapy. ASCO guidelines for appropriate chemotherapy dosing in obese patients conveyed in 2012 were also taken into account and incorporated. Additional biological and clinical information, including drug metabolism, PK and PD parameters in overweight/obese patients was summarized by the panel of experts.

Table 1. BMI classification according to the World Health Organization (WHO)

WHO classification	BMI (kg/m^2)
Underweight	BMI $\leq$ 19.9
Normal weight	20 $\leq$ BMI $\leq$ 24.9
Overweight	25 $\leq$ BMI $\leq$ 29.9
Obesity grade I	30 $\leq$ BMI $\leq$ 34.9
Obesity grade II	35 $\leq$ BMI $\leq$ 39.9
Obesity grade III	BMI $\geq$ 40

BMI, body mass index; WHO, World Health Organization.

BODY COMPOSITION AND CONVENTIONAL DEFINITIONS OF 'OVERWEIGHT' AND 'OBESITY'

According to the World Health Organization (WHO), 'overweight' and 'obesity' are defined as abnormal or excessive fat accumulation that presents a risk to health.[17]

In clinical practice, whether a person is overweight or obese is assessed by the BMI, calculated as weight (in kg) divided by height (in meters squared) and categorized using the following WHO classification (Table 1).

Unfortunately, BMI fails to take into account multiple important factors, including muscle mass, different distribution of adiposity and differences between races.[18] In addition, BMI is not used for children and adolescents aged 2-18 years for whom a percentile scale based on the child's sex and age is recommended. In this population, overweight is defined as a BMI between the 85th to 94th percentile, and obesity is considered for a BMI $\geq$95th percentile.[19] Despite these limitations, BMI is still the index most used in clinical practice for the categorization of overweight and obese patients (Figure 1).

For several anticancer drugs, doses are defined according to BSA. A variety of algorithms has been proposed for estimating BSA, though none of the currently available methods amounts to a universal standard. Each algorithm is fundamentally based on the patient's height and weight, with somewhat different theoretical, empirical or pragmatic

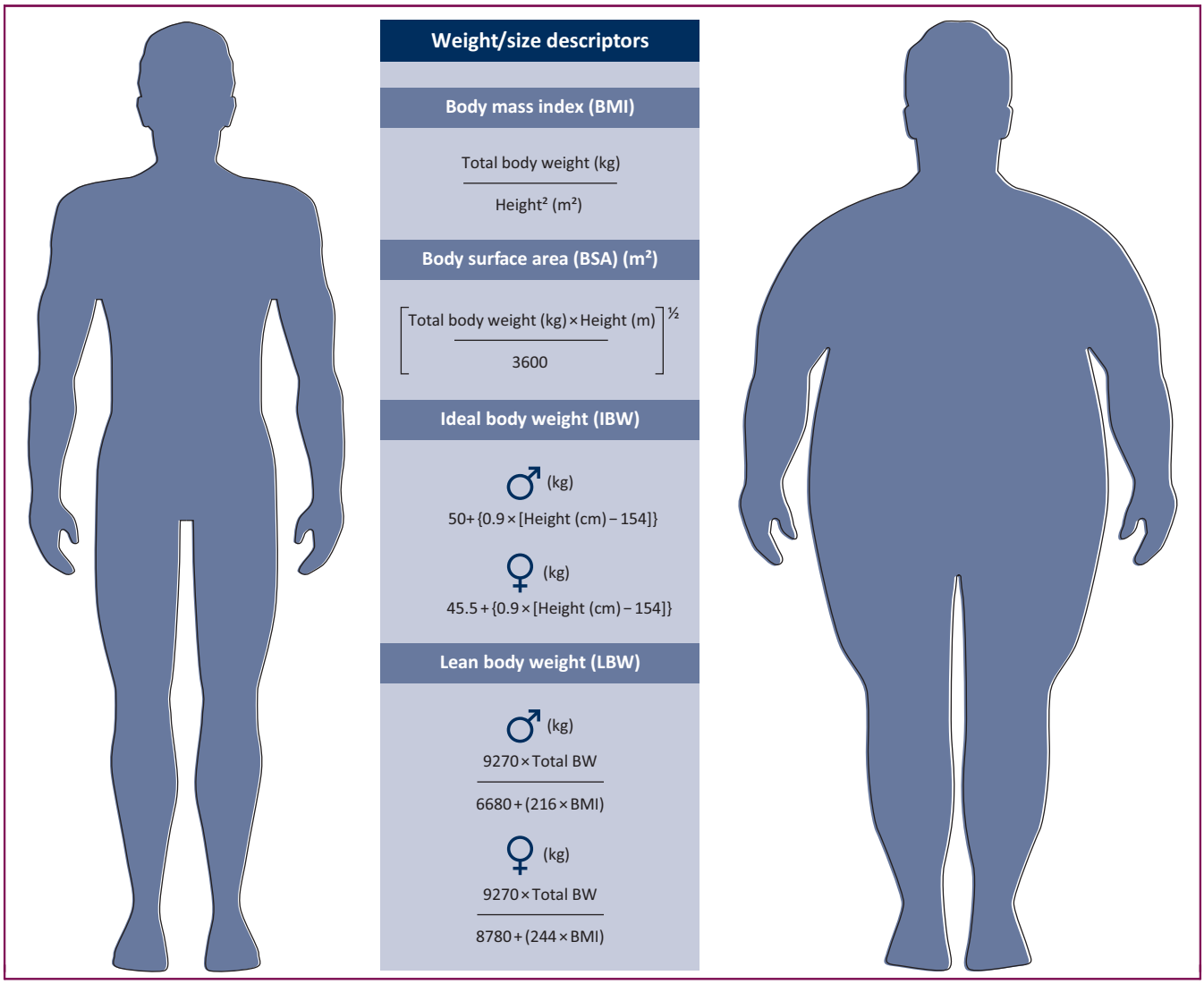

Figure 1. Summary of the most common weight and size descriptors and their limits.
Drug dose administration usually follows one of the three illustrated approaches: weight-based dosing, body-surface-area-based dosing, or fixed dosing. The first two strategies assume that drug PK parameters increase in proportion to increasing body size, whereas dosing drugs on a fixed basis presumes that body size does not influence drug PK parameters. Although commonly used to scale drug therapy in overweight or obese patients, each of these descriptors has important limitations. BMI and BSA are not informative as regards body composition and do not differentiate fat from lean tissue mass. IBW seems inappropriate as a dosing metric as it predicts the same dose for people of the same height, regardless of weight. LBW requires specialized equipment as it is measured with methods such as dual-energy X-ray absorptiometry, bioelectrical impedance analysis, underwater weighing and skinfold thickness.
BW, body-weight.

underpinnings.[20] Among them, the 'Mosteller' formula is commonly used (Figure 1).[21]

Although chemotherapy efficacy and toxicity are still highly variable between individual patients despite normalization based on BSA dosing, this approach is still the most accepted in oncology.[20] It should be noted that BSA, like BMI, is calculated on the basis of patient weight (kg) and height (cm), and is unable to distinguish between fat and lean tissue mass, so provides no information about body composition (Figure 1).

Alternative weight descriptors have been proposed to prevent drug overexposure with weight-based dosing, though each of these is associated with both benefits and limitations.[22]

Lean body weight (LBW) has also been recommended for scaling drug doses.[23] LBW reflects the weight of all 'non-fat' body components, including muscle and vascular organs such as the liver and the kidneys. As LBW contributes to ~99% of drugs clearance,[24] it might be useful for guiding dosing in obesity. However, although recent approaches (such as dual-energy X-ray absorptiometry, magnetic resonance imaging and computerized tomography) offer accurate information about body composition, these measures are only used for research purposes as they are expensive and have difficulty in accommodating individuals with BMIs at $\geq$35.[18] Predictive equations taking into account sex, body weight and height, have been proposed to quantify LBW, starting out from easily accessible patient characteristics (Figure 1).

Other convenient and affordable measures such as waist circumference, waist-to-hip ratio, bioelectrical impedance analysis (BIA) and skinfold thickness also have significant limitations.[18]

Finally, ideal body weight (IBW), which indirectly could represent LBW, is calculated as shown in Figure 1.[25] However, IBW seems inappropriate as a dosing metric because it predicts the same dose for people of the same height, regardless of weight. Furthermore, since limited variability exists when we consider height, dosing on IBW has the net effect of estimating a very narrow range of doses.[22]

Overall, the availability of disparate weight/size descriptors highlights the lack of a unifying gold-standard index to define chemotherapy dose adjustment in obese subjects. More clinically meaningful indexes should carefully consider the complex scenario defined by obesity itself, whose intricate changes in both fat and non-fat components profoundly influence the PK and PD of anticancer drugs.

EFFECTS OF OVERWEIGHT AND OBESITY ON PK PARAMETERS

Obesity plays a significant impact on key organs engaged in drug PK, with subsequent potential changes in all main PK parameters[13] (Figure 2).

Absorption

For the majority of tyrosine kinase inhibitors (TKIs) and for some cytotoxic molecules (e.g. capecitabine, vinorelbine and cyclophosphamide) administered orally, increases in gut perfusion and accelerated gastric emptying reported in obese subjects may contribute to enhancing their availability. Conversely, a decreased absorption rate may characterize drug treatments administered by subcutaneous and transdermal routes.[26] This may in part be explained by dysregulated blood flow in subcutaneous adipose tissue of obese individuals as a result of physiological adaptation to the increased adipose tissue mass and the reduced metabolic needs in obese individuals.[27,28]

Distribution

Classical PK parameters such as volume of distribution (Vd), clearance (Cl) and protein binding depend both on the physico-chemical properties of a drug (lipophilicity, polarity, molecular size and degree of ionization) and body composition, blood supply and plasma protein levels.[29-31]

Compared with molecules with weak or moderate lipophilicity, whose distribution in lean tissue is quite predictable, the majority of anticancer drugs are partly distributed in adipose tissues, and their affinity for plasma proteins and/or tissue components may change significantly in obese subjects. Given the unique properties of each drug, it is not surprising that obese and non-obese patients may have significantly different drug plasma concentrations even in the presence of similar tissue concentrations. For example, although the Vd for lipophilic drugs is expected to be higher in obese subjects, decreased tissue perfusion and cardiac function may result in lower Vd values.[29,32]

Obesity is characterized by an increase in both lean and fat mass. However, while the increased lean mass is responsible for 20%-40% of the excess weight, the percentage of fat mass can almost double in obese subjects. The lean mass per kg of body weight is therefore decreased in obese patients and this affects drug tissue distribution.[14] In addition, the potential role of the adipocytes on drug metabolism or on the specific activities that may characterize subcutaneous fat and visceral fat have not as yet been sufficiently investigated.[33] Especially in the case of subcutaneous administration, the distribution of a drug to and from a target in adipose tissue may be modified since the blood flow per gram of fat is significantly lower in obese patients compared with lean individuals.[34,35] For instance, in adipose tissue, the basal ethanol ratio was significantly higher and dialysate metabolite concentrations were significantly lower in obese than in non-obese men.[36] Subcutaneous adipose tissue blood flow (ATBF) is downregulated in obesity, and its responsiveness to meal intake is reduced; the reduction in ATBF represents an adaptation to the increased fat mass, probably mediated by adrenergic stimulation.[28] Furthermore, although plasma protein binding does not seem to be altered by body composition, the increased amount of alpha-1-acid-glycoprotein, linked to a chronic inflammatory state under conditions of obesity, may partially account for a prolonged half-life of some drugs.[34]

Cl is influenced by several factors including some that are unaffected by obesity (such as albumin binding and ionization status) and others potentially affected by obesity, including blood flow through the organ responsible for excretion (liver, kidney). In obese patients, liver steatosis may reduce blood flow through the liver and decrease Cl for several chemotherapy agents.[37] Renal Cl is dependent on the glomerular filtration rate (GFR), which may increase due to the increased cardiac output and tubular excretion/reabsorption, which is likely to be independent of body mass. In patients with nonalcoholic fatty liver disease (NAFLD), the cytochrome P (CYP) 3A4 activity and its abundance in human liver tissue has been studied and it was that CYP3A4-dependent metabolism that was reduced significantly, suggesting a negative impact of hepatic steatosis on drug metabolism.[38] Despite inconsistency on evaluation of creatinine, Cl does not seem to linearly correlate with total body weight in obese patients.[32]

Metabolism

The main site of metabolism is the liver, where drugs undergo transformation via phase I (biotransformation: oxidation, reduction and hydrolysis) and phase II (conjugation) reactions. Most parent drugs are active but a significant number of agents such as antimetabolites (e.g. antifolates, purines or pyrimidines derivatives) are prodrugs requiring activation in the liver to yield active metabolites. Liver abnormalities related to fatty infiltrations and steatosis combined with inflammation and fibrosis are proportionally correlated with the increasing BMI in obese subjects.[39] Inflammation may decrease the activity of specific CYP isoforms,[40,41] resulting in altered transformation and effectiveness of individual treatments. In addition, for drugs of high and moderate hepatic extraction, an increase in hepatic blood flow may enhance first-pass extraction in the liver as well as hepatic clearance.

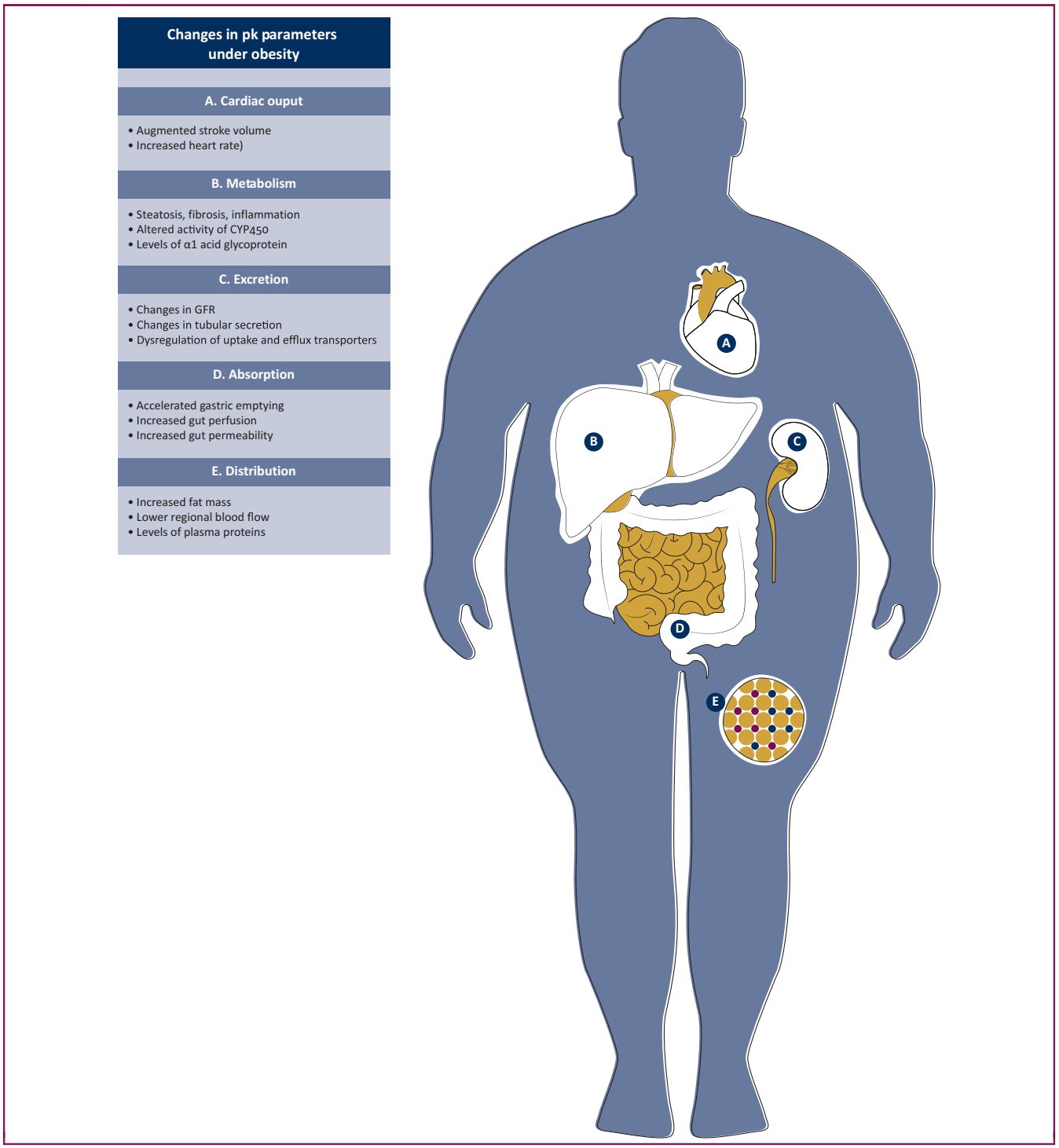

Figure 2. Graphic summary of the complex changes induced by obesity in all pharmacokinetic (PK) parameters.
The dose of each drug is determined by the plasma concentration required to achieve the desired effect. The plasma concentration of each drug following administration is dependent on its absorption (if not administered via the intravenous route), distribution, metabolism and excretion from the body. The duration of administration will also affect drug plasma concentration. In obese individuals, anthropometric changes in body proportions of water, fat and muscle mass are accompanied by variations in cardiac output, regional blood flow, alterations in liver and renal function and a chronic, low-grade inflammatory state.
GFR, glomerular filtration rate.

Elimination

Drugs are excreted as metabolites or unchanged. The effects of obesity on hepatic and renal drug clearance are still incompletely understood. However, increased cardiac output and hepatic blood flow and increased GFR may contribute to changes in the elimination of drugs in obese patients,[42] in particular since excess adipose tissue, blood volume, stroke volume and cardiac output are all increased to meet the metabolic demand of the excess adipose tissue. Concurrently, GFR may increase, although, in the long term, chronic renal dysfunction may occur with a resulting decline

in GFR being observed.[42] Similarly, obesity may interfere with biliary and renal secretion by dysregulating the expression and activities of tissue-specific uptake and efflux transporters.[43] For example, the metabolism of morphine is not altered in obese patients; however, decreased elimination of glucuronate metabolites is found, while a rational explanation for this finding is alterations in membrane transporter function and/or expression in the liver.[44] This suggests that pathophysiological changes associated with obesity may influence the activities of hepatic transporters and possibly contribute to an alteration in drug elimination rates.

Monoclonal antibodies (mAbs) differ significantly from chemical drugs in terms of PK parameters, showing low values for Cl and Vd, and a long half-life.[45] Both absorption and metabolism phases are almost non-existent; their distribution is mainly in the blood and extracellular fluids due to their size and hydrophilicity, while elimination occurs by intracellular degradation subsequent to their Fc receptor binding and target recognition specificities and, less frequently, by proteolytic catabolism.[46] The binding of mAbs to the target at the cell surface depends on tumor burden, expression levels of target and mAb affinity, while it is not affected by body weight. Conversely, proteolytic catabolism of mAbs targeting soluble targets taking place in endosomal space (accounting for 0.5% of the total tissue volume) is body-weight dependent, although its impact on total drug elimination is slight.[46] These common features suggest lower patient variability, though more studies, especially conducted in the early clinical phases, are needed to show the impact of overweight or obesity on their PK/PD profile.[46]

The availability of antibody-drug conjugates (ADCs) enlightens additional complexities.[47] The PK properties of ADCs should take into consideration the heterogeneity of these drugs and their composite structure, which gives rise to multiple active molecular species in systemic circulation and/or tissues of interest.

As briefly summarized, the question of obesity provides a tremendous challenge in the attempt to standardize dosing and for the achieving of consistent therapeutic effects while finding an acceptable or manageable level of toxicity in all patients. Clearly, in addition to the specific profile of each drug, the therapeutic intent, the type of tumor treated and the patient's age are all additional factors that must be taken into consideration.

EVIDENCE-BASED CHEMOTHERAPY DOSING IN OVERWEIGHT AND OBESE PATIENTS

The determination of optimal doses in oncology is often challenging both for chemotherapeutic and for targeted agents. Based on the theory according to which the highest tolerated dose of a drug should be that given for the best therapeutic effect to be achieved,[48] phase I and I/II clinical trials are currently designed to define the maximum tolerated dose (MTD) of novel molecules, whose schedules are further optimized in subsequent phase II-IV studies.[20,49]

By convention, chemotherapy unit dose administered per unit time is defined as 'dose intensity' (DI).[49] The delivery of optimal DI in potentially curable cancer patients has been proposed as a major indicator of cancer care quality.[20]

Dose-dense chemotherapy protocols (i.e. regimens in which the standard drug dose is delivered at shorter time intervals)[50] have been developed in recent years for some curable malignancies, such as early breast cancer,[51] based on the hypothesis that increased treatment frequency might kill a higher proportion of rapidly proliferating cells.[52]

The magnitude of chemotherapy dosing variations is generally quantified in terms of relative DI (RDI), namely the ratio of the delivered dose intensity to the standard (or planned) DI for a chemotherapy regimen.[49]

The importance of DI maintenance in oncology first emerged from pre-clinical studies involving murine models of sarcomas or carcinomas, in which two- to three-fold chemotherapy dose reductions correlated with significant worsening of complete response rates.[53]

In the clinical setting, an early study by Bonadonna et al. randomized 386 women with lymph-node-positive breast cancer to undergo either systemic adjuvant chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil, or follow-up after radical mastectomy. At the 20-year analysis, women receiving at least 85% of the planned chemotherapy dose experienced the best clinical outcome.[54] Additionally, a benefit of a higher chemotherapy dose was described by the Cancer and Leukemia Group B (CALGB) study 8541 and the French Adjuvant Breast Cancer Group,[55,56] suggesting the existence of a strong correlation between treatment dose and outcome in early breast cancer patients, in terms of disease-free survival and overall survival (OS), regardless of body weight. Chemotherapy dose reduction and treatment delays have also been shown to negatively impact on OS in metastatic breast, ovarian and lung cancer settings.[57-61]

Chemotherapy dose capping nevertheless often occurs in clinical practice, particularly among overweight and obese patients, in order to avoid toxicities. The use of idealized body weight or a maximum of 2.0 m^2 or 2.2 m^2 BSA instead of actual body weight in chemotherapy dose calculations is often planned from the start of treatment and based on empirical underpinnings.[8] Several retrospective studies in early-stage cancer patients reported that adjuvant chemotherapy dosage was often reduced in obese patients, with a subsequent negative impact on the clinical outcome.[7,9,62,63] Stocker et al.,[64] in an exploratory analysis of a PETACC 3 study, showed that dose reduction negatively affected relapse-free survival (RFS) [hazard ratio (HR): 0.48, 95% confidence interval (CI), 0.27-0.85; $P = 0.01$] with a strong trend toward better OS (HR: 0.53, 95% CI, 0.28-1.01; $P = 0.052$) in patients with BMI $\geq$30 kg/m^2 and BSA $\geq$2 m^2 receiving adjuvant chemotherapy for colon cancer.[9] Similarly, the CALGB study 8541 supports the use of full-dose chemotherapy compared with a reduced initial dose due to the improved failure-free survival in obese women (overall adjusted failure risk ratio of 0.73, 95% CI, 0.53-1.00).[63]

The likelihood of receiving a first-cycle dose reduction (<90% of the expected dose) increased in step with the obesity grade, being 11%, 20% and 37% in overweight, obese and severely obese patients, respectively, in a retrospective cohort study of 9672 breast cancer women treated with doxorubicin hydrochloride and cyclophosphamide.[7] However, the use of standard full-weight-based doses does not seem to be associated with a greater risk of adverse events in obese patients with respect to normal-weight patients in several retrospective analyses and observational studies.[7,63,65-74] Furthermore, a reduced risk of toxicity for events, such as leukopenia, neutropenia, thrombocytopenia and stomatitis, has been reported in some case series of weighty patients receiving full-dose chemotherapy, suggesting a BSA-related PK effect of BSA over drug elimination.[7,75-77] In particular, Wright et al. reported grade 3-4 leukopenia in 44% and 70% ($P = 0.0001$), and any grade thrombocytopenia in 27% and 50% ($P = 0.0004$) of ovarian cancer patients receiving carboplatin with BMI >30 kg/m^2 and BMI <25 g/m^2, respectively.[77] Likewise, Meyerhardt et al. showed lower rates of grade 3-4 leukopenia in heavier- compared with normal-weight patients (6% versus 11%, $P = 0.0036$) and any severe grade adverse events (45% versus 53%, $P = 0.04$).[75,76]

On the other hand, retrospective data from the randomized German Adjuvant Intergroup Node-positive (GAIN) study showed that dose-dense regimens (epirubicin, docetaxel and cyclophosphamide or epirubicin and cyclophosphamide followed by docetaxel plus capecitabine) at full dose according to the actual BSA in obese breast cancer patients correlated with a higher risk of severe toxicities, such as febrile neutropenia, high-grade thrombocytopenia and thromboembolic events, as compared with obese patients receiving an adjusted dose (16% versus 6%, $P = 0.003$; 9% versus 3%, $P = 0.002$; 17% versus 10%, $P = 0.017$, respectively). The authors therefore suggested a dose adjustment of intense dose-dense chemotherapy in obese patients to avoid the occurrence of life-threatening complications.[78]

A systematic review and meta-analysis attempted to reveal the risks and benefits of full-dose chemotherapy in obese patients.[79] Twelve studies involving 9314 patients with colorectal cancer (55%), breast cancer (29%) or other types of tumors were analyzed to compare toxic effects and survival in obese and normal-weight patients treated according to the actual BSA. In most of these studies, toxicity and outcome did not statistically differ between the two groups. Quantitative pooling of the available data showed that the rates of toxic effects were similar or lower in obese patients [any grade 3/4 toxic effect: odds ratio (OR) 0.75, CI 0.65-0.87]. Among eight studies comparing progression-free survival and OS, Jones et al. showed that obese patients with B-cell non-Hodgkin's lymphoma and treated with seven different chemotherapy regimens (mostly, CHOP backbone) reported longer survival compared with normal-weight subjects.[80] Conversely, Meloni et al. reported a benefit in normal-weight patients undergoing conditioning regimens with busulfan/cyclophosphamide for autologous stem cell transplantation.[81]

BSA however, taking into account weight and height, has not been deemed a proficient parameter for determining the optimal dose of chemotherapy.[82] Indeed, body composition, considering muscle and adipose tissue distribution, seems to better reflect the complexity of the anthropometric features of cancer patients (such as obesity, sarcopenia and myopenia). A body of evidence suggests that lower LBW was associated with higher toxicity, while greater adiposity was associated with lower anthracycline and taxane-based chemotherapy adherence (RDI), irrespective of BSA.[83,84] The lower muscle mass reduced the clearance of hydrophilic drugs, such as doxorubicin, resulting in a risk of overdose and increased toxicity.[85,86] On the other hand, lipophilic compounds, such as paclitaxel and docetaxel, could accumulate in fat tissue with resulting delayed toxicity.[87] Overall, body composition may be useful for predicting higher toxicity risk. Large prospective clinical trials with planned analysis of body composition and pharmacokinetic data are needed to provide evidence both as regards adverse events and efficacy.

ASCO guidelines for chemotherapy dosage in overweight/obese patients

To date, the only recommendations available for the management of overweight patients derive from ASCO guidelines published in 2012, which do not consider novel molecular-targeted therapies and immunotherapies. ASCO carried out a systematic literature search and review providing clinical practice guidelines on appropriate chemotherapy dosing in obese cancer patients. The expert panel recommended full-weight-based chemotherapy doses in the treatment of the obese cancer patient, particularly when cure is the goal of treatment. Moreover, the guidelines suggested treatment-related toxicities in obese cancer patients should be treated as in normal-weight patients. If a dose reduction is needed to limit toxicity, consideration should be given to the resumption of full-weight-based doses for subsequent cycles, especially if the putative cause of the observed toxicity (e.g. impaired renal, hepatic function) has been resolved.[8]

TARGETED THERAPIES AND IMMUNE CHECKPOINT INHIBITORS IN OVERWEIGHT AND OBESE PATIENTS

Compared with chemotherapy drugs, mAbs are generally not influenced by body size and composition in terms of their distribution and elimination, requiring fewer dosage variations unless clinically meaningful toxicities occur.[88] Indeed, the change in Vd and in blood volume (BV) of mAbs is less significant than the change in body weight. In underweight patients, however, the reduction in BV could result in lower plasma levels of body-size-based dosing mAbs, while the greater BV in obese patients could result in higher plasma levels of the drug. Conversely, in flat-fixed dosing strategies, the underweight and obese patients could receive a relatively higher and lower dose, respectively.[88] This interpatient variability gave rise to the comparison between body-size-based or fixed dosing of mAbs.

In particular, immune checkpoint inhibitors (ICIs) are characterized by a wide therapeutic index, for which fixed dosing has been introduced in clinical practice to reduce both errors and preparation costs.[89,90]

Nevertheless, the limited number of PK/PD studies on ICIs means there remain doubts about the existence of a potential relationship between the dose required and body weight for some of them.[91] For instance, the clearance of ipilimumab increases with increasing body weight, making a body-weight normalized dosing regimen more appropriate than a fixed dose for this anti-CTLA-4.[92] Similarly, the clearance of nivolumab might be influenced by high body weight resulting in lowest drug exposures.[93,94] However, Bajaj et al. reported that nivolumab steady-state exposure seems to be comparable over the evaluated body weight ranges (from 34.1 to 168.2 kg). Thus the variation is not expected to be clinically relevant.[93] According to a population PK analysis, total systemic clearance of avelumab also increases with body weight, whereas age, gender, race, programmed death-ligand 1 (PD-L1) status, tumor burden, renal impairment and mild or moderate hepatic impairment do not.[95] Similarly, body weight seems to be significantly associated with varying clearance also for pembrolizumab, cemiplimab, atezolizumab and durvalumab even if the clearance variation does not appear clinically significant for all of them (effect on PK parameter does not exceed 30%).[96] Thus, weight-based dosing seems to be appropriated for anti-programmed cell death protein 1 (PD-1) and anti-PD-L1 even in overweight and obese patients.

On the other hand, the flat dose regimens are approved for nivolumab and pembrolizumab, considering the former body-weight-based doses for 80 kg and 100 kg patients, respectively. The recommended dosages were approved according to population PK modeling showing a substantial overlap of exposure between body-weight-based and fixed dose with a comparable efficacy and safety profile.[89,97,98] However, to date, the risk of reduced exposure cannot be ruled out for heavier patients, legitimizing questions as to the generalization of flat doses as opposed to body-weight-normalized doses.[92,96] Even if some data published in the literature show a dependence of the PK of ICIs on the characteristics of patients, their consistency is not sufficiently robust to justify dose adjustment of ICIs in overweight/obese subjects.

There is a huge body of evidence suggesting the potential link between obesity and prognosis in patients receiving ICIs, highlighting the role of proper dosing strategy to maximize drug efficacy.[99]

Indeed, chronic inflammatory state and consequent T-cell exhaustion observed in both obese murine models and humans have been shown to correlate with suppressed immune responses.[100] On the other hand, leptin secretion, typically increased in obese subjects,[101] has been associated with increased tumor cell proliferation and cancer infiltration by PD-1-expressing lymphocytes. In pre-clinical studies, administration of anti-PD-1 agents resulted in increased tumor shrinkage and reduced metastasis formation in obese versus control murine melanoma models.[102]

In the clinical setting, several retrospective studies explored the impact of BMI on the clinical outcome of cancer patients who underwent treatment with ICIs.[103-105] Among these, Richtig et al. described a significantly higher response rate (RR) and lower incidence of brain metastases in patients with BMI $\geq$25 kg/m^2 treated with 3 mg/kg ipilimumab, in the absence of significant differences in terms of side-effects, compared with the normal-weight group ($P = 0.498$, χ^2 test).[105] A wide multi-cohort analysis including data from 1918 patients receiving chemotherapy, immunotherapy or targeted treatment of metastatic melanoma confirmed the association between obesity and OS, although this correlation was restricted to males who underwent treatments other than chemotherapy.[103] The authors suggested that such discrepancy between sexes might be explained, at least partially, by differences in the hormonal milieu and body composition. Notably, there was no safety profile difference between patients with normal and with high BMIs across different regimens. A recent retrospective study explored the correlation between obesity and clinical outcome not only in melanoma, but also in lung and renal cell carcinoma, confirming better clinical outcomes in terms of OS and progression-free survival (PFS) in patients with a BMI $\geq$25 kg/m^2 treated with first-line PD-1/PD-L1 inhibitors.[106] In this study, overweight/obese patients turned out to be more likely to experience any grade immune-related adverse events (irAEs) as against non-overweight patients (55.6% versus 25.2%, respectively; $P < 0.0001$), but no differences were observed between the two groups in terms of grade 3-4 irAEs (7.6% versus 5.3%, $P = 0.1338$). Two wider meta-analyses, including 13 and 16 studies on ICIs, respectively, have further confirmed the favorable prognostic significance of high BMI with respect to OS and PFS.[107,108] The former study described no significant differences between obese/overweight patients and normal-weight patients for all-grade irAEs (overweight versus normal: pooled RR = 1.28, 95% CI 0.76-2.18, $P = 0.356$; obese versus normal: pooled RR = 1.36, 95% CI 0.85-2.17, $P = 0.207$),[107] while the latter showed a significantly higher risk of adverse events in high- versus low-BMI subjects (OR = 2.91, 95% CI 1.39-6.11; $P = 0.005$).[108] It is of note that none of the above mentioned studies reported ICI dose adjustment in overweight/obese subjects.

Such data led to the coining of the term 'obesity paradox', namely the apparently favorable correlation between overweight/class I obesity and prognosis in cancer patients undergoing treatment with ICIs,[99,109] whose underlying biological mechanisms have, however, yet to be elucidated. In this regard, a putative explanation was proposed by Sanchez and coworkers who analyzed the gene expression profile of primary tumors and peritumoral fat derived from renal clear-cell carcinoma patients with variable BMI. Interestingly, the extent of immune cell infiltration did not significantly differ according to the patients' BMI, but up-regulation of Th1 and Th2 pathways, dendritic cell maturation and CD28 signaling were found in samples from obese versus normal-weight patients.[110] Higher angiogenic scores on gene-set enrichment analyses were moreover found in the tumors of obese patients, suggesting a

potential higher sensitivity of these malignancies to angiogenesis inhibitors.[110]

With respect to anti-angiogenic drugs, conflicting data emerged with regard to the correlation between obesity and treatment outcomes. For instance, a study from Miyamoto et al. on bevacizumab in metastatic colorectal cancer showed a significant correlation between increased visceral fat and longer OS ($P = 0.03$),[111] whereas a BMI $\geq$25 kg/m^2 was found to positively impact on both PFS and OS ($P < 0.05$ in both instances) in metastatic HER2-negative breast cancer patients treated with first-line bevacizumab plus paclitaxel.[112] Other studies, however, showed a negative correlation between high BMI and clinical outcome in metastatic colorectal cancer patients,[113,114] particularly in those with KRAS wild-type left-sided primary tumors, receiving bevacizumab in addition to chemotherapy.[113]

As for other mAbs, in non-metastatic HER2-positive breast cancer, a recent report from Gonzalez Garcia et al. has suggested that the administration of trastuzumab via subcutaneous injection allows the target concentration of 20 μg/ml to be reached in 87.5% of patients with BMI $\leq$30 kg/m^2, compared with only 20% of women with BMI $>$30 kg/m^2 ($P < 0.001$). By contrast, the proportion of patients reaching the target concentration after intravenous trastuzumab administration has been independent of their BMI. Though based on a small patient series ($N = 50$),[115] this study highlights the need for further investigation on this topic to ensure adequate drug exposure in this population suffering from potentially curable cancer.

With respect to TKIs and other targeted agents, the impact of the patient being overweight or obese on the treatment outcome was investigated in 1975 patients from the International Metastatic Renal Cell Carcinoma Database Consortium. Interestingly, a BMI $\geq$25 kg/m^2 was found to be associated with improved OS (25.6 months, 95% CI 23.2-28.6 versus 17.1 months, 95% CI 15.5-18.5) in advanced clear-cell renal cell carcinoma patients.[116] The cumulative incidence of treatment failure due to toxicity did not differ between the overweight/obese (13%, 95% CI 10%-17%) and underweight/normal groups (15%, 95% CI 12%-19%).[116] Bergerot et al. have recently described a similar trend on a smaller case series.[117]

In metastatic EGFR-mutated non-small cell lung cancer (NSCLC), however, no correlation has been found between patient nutritional status (defined by BMI, body weight and BSA) and response to gefitinib,[118] whereas a potential higher risk of grade $\geq$2 hepatic dysfunction has been observed in overweight subjects.[119]

As for other targeted agents, BMI did not impact on molecular RR of nilotinib and dasatinib, while a delayed and low rate of molecular responses were observed for imatinib as frontline treatment in obese patients, probably due to the effect of the drug on signaling regulation of macrophages via platelet-derived growth factor (PDGF) receptors adipogenesis stimulation.[120] Interestingly, blood levels of imatinib after bariatric surgery in an obese patient were 40%-60% lower than before operation.[121]

A study on renal cell carcinoma patients treated with cabozantinib, stratified by BMI, showed that a BMI $\geq$25 correlated with longer survival. Although the PK of cabozantinib was not examined, the study suggests that BMI may be considered a prognostic biomarker for advanced renal cell carcinoma.[122]

As regards regorafenib, a multi-kinase inhibitor administered to patients with several solid tumors, covariate analysis identified sex and BMI as impacting exposure to regorafenib; however, the changes observed in PK were rather limited and neither single nor combined covariates predicted exposures that would warrant a priori regorafenib dose adjustment.[123]

Finally, a case report found that in a patient with severe obesity, plasma levels of sunitinib were below clinical active level, and thus individual therapeutic drug monitoring is required for optimal guidance of treatment.[124]

Among the ADCs, a retrospective study included adult patients with breast cancer receiving T-DM1 and the primary endpoint was the incidence of T-DM1 treatment modifications secondary to an adverse event. Treatment modifications and delays due to toxicity were significantly more frequent in obese patients compared with non-obese subjects. Left ventricular ejection fraction decrease, bilirubin increase, thrombocytopenia and peripheral neuropathy were also significantly increased in the obese population compared with controls. This study suggests that obese patients receiving T-DM1 may require more accurate treatment monitoring for adverse events,[125] although the data are not sufficiently robust to recommend interventions other than careful follow-up.

In conclusion, conflicting data are emerging on the onset of adverse events in overweight/obese patients treated with ICIs administered at standard doses, but there is a huge body of evidence suggesting the lack of a negative impact of high BMI on clinical outcome in this setting. By contrast, data on targeted molecules are much more heterogeneous, even within the same drug class, confirming the complexity of such a clinical condition and suggest the need for prospective clinical studies to uniquely define to what extent obesity can impact treatment choices, dosing and outcomes in cancer patients eligible for novel anticancer drugs.

EXPERT OPINION ON DOSAGE OF ANTICANCER DRUG IN OVERWEIGHT AND OBESE PATIENTS

Ethical issues limit the carrying out of RCTs that compare full-weight-based versus adjusted dose of anticancer drugs in obese patients. These recommendations are thus based on observational studies and subgroup analyses of RCTs evaluating safety and efficacy profiles in heavy patients as compared with those of normal weight.

Question 1: is BSA the best approach for cytotoxic chemotherapy dosing?

BSA dosing is the most highly endorsed approach in clinical practice for chemotherapy drugs. The lack of excess toxicity

in obese patients receiving BSA-based dose chemotherapy supports the reliability of this approach despite its acknowledged limitations. The BSA formula does not consider the patient's sex and body composition, leaving out the complexity of the cancer patient typified by increased fat mass associated with sarcopenia. Nevertheless, the actual tools of body composition analysis, such as anthropometry, are accurate. These alternative dosing methods are currently therefore limited to clinical studies.

Question 2: is a dose adjustment of cytotoxic chemotherapy required in obese patients?

To date, there has been no evidence that full-weight-based dosing of chemotherapeutic agents increases the toxicity profile for obese patients, while outstanding evidence indicates the role of DI on clinical outcome. The panel of experts therefore recommends avoiding empirical dose reduction of chemotherapy agents in the absence of other comorbidities associated with obesity. In patients receiving dose-dense regimens, careful clinical monitoring should be considered.

Question 3: is a dose adjustment of targeted therapy and ICIs required in obese patients?

Conflicting data on targeted molecules (even within the same class) do not at present permit univocal recommendations: in most cases, individual therapeutic drug monitoring is required for optimal guidance of treatment. mAbs have a wide therapeutic window, while body size contributes little to exposure variability. The high body weight increases the ICIs clearance without a clinically relevant effect. Therefore, no dosing variations are recommended for overweight or obese patients eligible for ICIs.

The unique properties of ADCs suggest the need for careful monitoring of obese patients undergoing treatment with these agents, but more specific recommendations are at present unattainable.

Question 4: what is the best schedule for dosing mAbs in obese patients?

To date, most approved mAbs are dosed at body-size-based schedules (milligram per kg or BSA-based), while only selected drugs are approved for flat-fixed dosing use. The molecules with a meaningful effect of body weight on Vd and Cl, have less interpatient variability using fixed-dose method than is the case with body-size-based dosing. Nevertheless, the risk of reduced exposure of anti-PD-1 and anti-PD-L1 cannot be ruled out for heavier patients. Therefore, PK/PD and dose-response clinical analyses are needed to support the wider use of fixed dose of mAbs thus reducing medication errors and health care costs.

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