DOSAGE OF CISPLATIN AND RELATED TOXICITY OF CANCER PATIENTS BASED ON BODY FAT AND MUSCLE MASS

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Abstract

In oncology practice, the human body surface area (BSA) is used for the calculation of the dose of chemotherapy. The human BSA is determined by derived formulas, but it is not directly linked to the pharmacokinetics of the drugs. Obesity alters the disposition of drugs pharmacokinetics, which should be considered when prescribing medications in this patient population. Failure to adjust doses in obesity may result in increased toxicity. The aim of this study was to assess predictors of an increase in the level of trygliceride considered to be among the cardiovascular risk factors.

Method. The study involved 118 oncology patients with various tumor localizations. The patients underwent anthropometric measurements (height, weight, circumference, fat fold thickness, the distance between the epicondyls above the joint), and the BSA (according to the Mosteller formula). Patients who received cisplatin chemotherapy were analyzed in serum triglyceride levels before and after the treatment.

Results. A comparison of female and male subsamples revealed no significant in variance between sexes and no significant differences in initial triglyceride, triglyceride change, and in the age between groups. Body fat mass was relatively higher in females, while body muscle mass and bone

mass were relatively higher in males. There was a difference in the cisplatin dose, with a higher dose for males than for females. The results demonstrate that the higher cisplatin dose and higher body fat mass are significant predictors of an increase in triglyceride for both sexes.

Keywords: Body surface area (BSA), chemotherapy, cisplatin, body fat mass, triglycerides

Introduction:

Platinum-based drugs are widely used anticancer agents with a broad range of antitumor activities. *Cisplatin* [cis-diamminedichloroplatinum(II)] has a significant activity in ovarian, testicular, colon, bladder, head and neck, and lung cancer, where it is most commonly used in combination with other drugs (Loehrer & Einhorn, 1984); (Yoon et al., 2011). A cytotoxic drug appears to have alkylation action and to possess antitumor activity. Thus, it has become one of the most successful anticancer drug used worldwide in almost 50% of solid tumor chemotherapies. One of the major problems of antineoplastic chemotherapy refers to the high toxicity of antitumor drugs. In order to reduce their negative influence on healthy cells of a body and enhance the efficacy of therapy (Yaroshenko, Grigoriev, Sidorova & Kartsova, 2013). Although the initial response rates can be high with cisplatin-based regimen, the clinical utility of the drug is often limited by the onset of acquired or intrinsic resistance (Wang & Lippard, 2005) and the number of side effects such as kidney damage, vomiting/nausea, and neurotoxicity.

With approximately one-third of Americans now being obese (as defined by a body mass index, or BMI, $\geq$30 kg/m^2) (Flegal, Carroll & Ogden, 2010), by determining appropriate methods for dosing chemotherapy in obese patients, it is important to ensure safe and effective cancer care for an increasingly large segment of the population (Hourdequin, Schpero, McKenna, Piazik & Larson, 2013). In adult patients with cancer, drug dosing has traditionally been based on a patient's estimated body surface area (BSA) (Freireich, Gehan & Rall, 1966). The most commonly used Mosteller formula for BSA calculation was also used in this study.

There exists a compelling evidence that reductions from a standard dose and dose-intensity may compromise disease-free survival (DFS) and overall survival (OS) in the curative setting (Lyman, 2011). Furthermore, a number of authors have suggested that the optimal delivery of cancer chemotherapy should be considered an indicator of quality of care (Griggs, et al., 2012)**.**

Since 1950's, researchers have used body surface area (BSA), a number determined by a person's height and actual body weight (ABW).

Problems arise when patients are obese, as dose calculations based on BSA can be very high. Many practitioners, fearing excess toxic effects with such large doses, respond by reducing the doses of chemotherapy given to obese patients. Clinical practice varies significantly, both in terms of whether doses are reduced and, if so, how this is done (Griggs, Sorbero & Lyman, 2005); (Lyman, 2011).

The obesity has been associated with poorer survival in many cancers, including breast, colon, ovarian, and prostate cancers (Efstathiou, Bae & Shipley, 2007); (Lu, Ma & Malone, 2011); (Meyerhardt, Catalano & Haller, 2003); (Boyd, Campbell & Germanson, 1981); (Newman, Lees & Jenkins, 1997); (Zhang, Xie & Lee, 2005); (Pavelka, Brown & Karlan, 2006); (Litton, Gonzalez-Angulo & Warneke, 2008); (de Azambuja, McCaskill-Stevens & Francis, 2010). While this poorer survival is multifactorial, there is some evidence to suggest that chemotherapy under dosing in obese patients may be contributing to these worse outcomes. Regardless of body weight, reducing the dose intensity of chemotherapy has been shown to negatively impact survival in multiple cancer types (Wildiers & Reiser, 2011); (Wood, Budman & Korzun, 1994); (Bonadonna & Valagussa, 1981). Despite studies confirming the safety and importance of full weight– based cytotoxic (intravenous [IV] and oral) chemotherapy dosing, many overweight and obese patients continue to receive limited chemotherapy doses (Lyman, Dale & Crawford, 2003); (Greenman, Jagielski & Griggs, 2008); (Griggs & Sabel, 2008); (Griggs, Sorbero & Lyman, 2005).

Practice pattern studies demonstrate that up to 40% of obese patients receive limited doses that are not based on actual body weight.

A triglyceride (TG, triacylglycerol, TAG, or triacylglyceride) is an ester derived from glycerol and three fatty acids (IUPAC-IUB Commission on Biochemical Nomenclature (CBN), 2007). As a blood lipid, they help enable the bidirectional transference of adipose fat and blood glucose from the liver. There are many triglycerides: depending on the oil source, some are highly unsaturated, some so. Triglycerides are formed by combining glycerol with three molecules of fatty acid. Fat and liver cells can synthesize and store triglycerides. When the body requires fatty acids as an energy source, the hormone glucagon signals the breakdown of the triglycerides by hormone-sensitive lipase to release free fatty acids.

Triglycerides cannot pass through cell membranes freely. Special enzymes on the walls of blood vessels, called lipoprotein lipases, must break down triglycerides into free fatty acids and glycerol. Fatty acids can then be taken up by cells via the fatty acid transporter (FAT).

In the human body, high levels of triglycerides in the bloodstream have been linked to atherosclerosis and, by extension, the risk of heart disease and stroke. The relative negative impact of raised levels of

triglycerides compared to that of Low-density lipoprotein (LDL): high-density lipoprotein (HDL) ratios are as yet unknown. The risk can be partly accounted for by a strong inverse relationship between triglyceride level and HDL-cholesterol level. Triglycerides are considered to be among the cardiovascular risk factors (Strumberg et. al., 2002).

Therefore, control for triglycerides in the blood during the treatment seems an important feature for understanding pharmacokinetics of drugs. At the same time, anthropometry allows to assess body muscle, bone and fat mass. Taking into account an opportunity provided by anthropometric methods, the aim of this study was to assess body muscle, bone, and fat mass, a dose of cisplatin, and an initial triglyceride level as predictors of an increase in the level of triglycerides (Table 1.).

Table 1. Criteria proposed for clinical diagnosis of elevated triglyceride levels under fasting conditions (Berglund et. al., 2012)

NCEP ATP III[(a)]			**The Endocrine Society 2010[(b)]**		
Normal	<150 mg/dl	<1.7 mmol/liter	**Normal**	<150 mg/dl	<1.7 mmol/liter
Borderline-high triglycerides	150–199 mg/dl	1.7–2.3 mmol/liter	Mild hypertriglyceridemia	150–199 mg/dl	1.7–2.3 mmol/liter
High triglycerides	200–499 mg/dl	2.3–5.6 mmol/liter	Moderate hypertriglyceridemia	200–999 mg/dl	2.3–11.2 mmol/liter
Very high triglycerides	≥500 mg/dl	≥5.6 mmol/liter	Severe hypertriglyceridemia	1000–1999 mg/dl	11.2–22.4 mmol/liter
			Very severe hypertriglyceridemia	≥2000 mg/dl	≥22.4 mmol/liter

[a]NCEP ATP III - National Cholesterol Education Program Adult Treatment Panel

[b]The criteria developed for the present guidelines focus on the ability to assess risk for premature CVD (cardiovascular disease) **vs.** risk for pancreatitis. The designations of **mild** and **moderate** hypertriglyceridemia correspond to the range of levels predominant in risk assessment for premature CVD, and this range includes the vast majority of subjects with hypertriglyceridemia. Severe hypertriglyceridemia carries a susceptibility for intermittent increases in levels above 2000 mg/dl and subsequent risk of pancreatitis; very severe hypertriglyceridemia is indicative of risk for pancreatitis. In addition, these levels suggest different etiologies. Presence of mild or moderate hypertriglyceridemia is commonly due to a dominant underlying cause in each patient, whereas severe or very severe hypertriglyceridemia is more likely due to several contributing factors.

Methods:

The study involved 118 oncology patients.There were 34 females aged from 42 to 79 years (median age 64 years) and 84 males aged from 28 to 84 (median age 65 years). The median age of patients at the time of our study was 64 years. The sample consisted of patients with cancer of any type, receiving chemotherapy based on BSA. BSA was calculated in

accordance with the Mosteller formula: BSA (m^2) = [Ht(cm) * Wt(kg) / 3600]^{½}, where Ht - height (cm), Wt- body weight (kg).

The body mass index, defined as body weight (kg) divided by height squared (m^2), was used as a measure of obesity. We included patients who met the criteria: reported according to obese (BMI ≥30 kg/m^2) and normal weight (BMI 18.5–24.9 kg/m^2) categories, as defined by the 1995 WHO criteria (Cole, Bellizzi, Flegal, & Dietz, 2000). In our study, 5% of patients had a BMI below 18.5kg/m^2, 40% of the normal weight range, but 31% of 25-30 kg/m^2 and 24% of cases of obesity (over 30 kg/m^2).

Anthropometry: Body anthropometric parameters in cancer patients were used as scales, measuring tapes, anthropometers (gauge height) and calliper.

Adipose tissue (passive) mass of the formula:

$$D = 1{,}3 \times \frac{100 + W + (H - 160}{100} \times \frac{(d_1 + d_2 + d_3 + d_4 + d_5 + d_6)}{12} \qquad (1)$$

where: D - fat mass (kg), W – body weight (kg), H – height (cm), d – fat fold thickness (mm) on the upper arm, forearm, thigh, lower leg, the ribs and abdomen.

Active muscle mass of the formula:

$$M = 6{,}5 \times H \times \left(\frac{E_4}{25{,}12} - \frac{E_5}{100} \right)^2 \times 10^{-3} \qquad (2)$$

where: **M** - muscle mass (kg), $\mathbf{E_4}$ lower arm + forearm + Upper + Lower the amount of girth (cm), $\mathbf{E_5}$ fat fold - 5 fold the amount of fat (2 arm + forearm + Upper + Lower) (mm), **H** - height (cm)

Bone mass of:

$$O = 1{,}25 \times H \times \left(\frac{E_{4epi}}{4} \right)^2 \times 10^{-3} \qquad (3)$$

where: **O** – bone mass (kg), **H** - height (cm) $\mathbf{E_{4epi}}$ - the distance between epicondil amount (arm epicondil + forearm + Upper + Lower) (cm).

Adipose tissue, muscle, bone mass determination in relative terms (%) was carried out according to the formulas:

$$\text{Adipose tissue mass}(\%) = \frac{\text{D} \times 100}{\text{W}} \qquad (4)$$

$$\text{Muscule mass}(\%) = \frac{\text{M} \times 100}{\text{W}} \qquad (5)$$

$$\text{Bone mass}(\%) = \frac{\text{O} \times 100}{\text{W}} \qquad (6)$$

where: W- body weight (kg)

The Medium build body tissue composition in relative terms (%) is given in Table 2.

Table 2. Medium build body tissue composition in relative terms (%)

Gender	Adipose tissue mass	Muscule mass	Bone mass
Male	12.63 -16.29	32.91 – 35.18	10.77 – 12.88
Female	19.60 -24.21	23.69 – 25.64	8.64 – 9.61

In patients who received cisplatin (75 mg/m^2) chemotherapy was analyzed in serum triglyceride levels before and after treatment. All blood samples and triglycerides were analyzed according to laboratory standards at Pauls Stradins University Hospital and standard normal ranges were used in patients receiving of cisplatin after intravenous (i.v.) administration.

Results:

In order to assess predictors of triglyceride change in the research sample, the analysis was performed in three steps: a comparison of female and male subsamples, correlation analysis, and a regression analysis.

Table 3 presents descriptive statistics and comparison of means in females and males.

Table 3. Descriptive statistics and comparison of means between sexes

	Males (n = 84)	Females (n = 34)	
Measures	M (SD)	M (SD)	t-test
Age, years	62.51 (11.16)	62.68 (10.23)	-0.07
Fat mass	10.85 (4.77)	14.27 (5.04)	-3.43**
Muscle mass	28.27 (5.52)	25.23 (6.20)	2.61*
Bone mass	13.53 (1.67)	10.40 (1.41)	9.59***
Cisplatin dose (mg)	130.30 (21.08)	122.21 (14.83)	2.04*
Initial triglyceride (mmol/l)	1.22 (0.39)	1.19 (0.32)	0.28
Change of triglyceride(%)	0.58 (0.44)	0.52 (0.39)	0.66

*** p< 0.001. ** p<0 .01. * p<0 .05.

It should be noted that Levene's test for equality of variations demonstrated no significant differences in variance between sexes. Student's t-test demonstrated no significant differences in initial triglyceride, triglyceride change, and in age between groups. Body fat mass was higher in females, when body muscle mass and bone mass were higher in males. In addition, there was a difference in the cisplatin dose, with a higher dose for males than for females ($p < 0.001$).

Pearson product-moment correlations indicated positive correlations of change of triglyceride with the cisplatin dose, initial level of triglyceride

and body fat, muscle, and bone mass ($p<0.001$) (Table 4). At the same time, there were no significant correlations between the change of triglyceride and age or sex.

Table 4. Correlations among triglyceride, cisplatin dose, anthropometric measures, age, and sex (n = 118).

	1.	2.	3.	4.	5.	6.	7.	8.
1. Change of triglyceride	-							
2. Cisplatin dose	0.50***	-						
3. Initial triglyceride	0.32***	0.45***	-					
4. Fat mass	0.47***	0.16	0.41***	-				
5. Muscle mass	0.48***	0.33***	0.52***	0.60***	-			
6. Bone mass	0.34***	0.24*	0.39***	0.17	0.64***	-		
7. Age	-0.15	-0.23*	-0.12	-0.03	-0.22*	-0.07	-	
8. Sex	-0.06	-0.19*	-0.03	0.31**	-0.24*	-0.67***	0.01	-

Note. Males and females were coded as 1 and 2, respectively.
*** p< 0.001. ** p<0.01. * p<0 .05.

To answer the question about the predictors of a toxic effect, a standard multiple linear regression was performed with a change of triglyceride as an independent variable and the cisplatin dose ($p <0.001$), initial triglyceride, body fat mass, muscle mass, and bone mass as dependent variables. Despite the absence of a significant correlation, sex was included into analysis as a dependent variable in order to control its effect on the model. Table 5 displays regression coefficients and an evaluation of the model.

Table 5. Standard multiple linear regression of triglyceride change on the cisplatin dose, initial triglyceride, sex, body fat, muscle, and bone masses (n=118)

Predictors	B	SEB	β
Cisplatin dose	0.01	0.00	0.43***
Initial triglyceride	-0.18	0.10	-0.16
Fat mass	0.03	0.01	0.31**
Muscle mass	0.02	0.01	0.20
Bone mass	0.03	0.03	0.14
Sex	0.03	0.11	0.03
Model: $F(6, 112) = 15.94$, $p < 0.001$; $R^2 = 0.47$, adjusted $R^2 = 0.44$.			

*** p< 0.001. ** p<0 .01.

The higher cisplatin dose contributed significantly to the increase of triglyceride. Higher body fat mass also predicted an increase of triglyceride. Body muscle mass, bone mass, initial triglyceride, and sex did not contribute significantly to the model.

Discussion:

The results demonstrate that the higher cisplatin dose and higher body fat mass are significant predictors of an increase in triglyceride. In our study, taking into account the American Heart Association guidelines triglyceride levels corresponded to slightly above normal. Since patients are receiving chemotherapy courses, increase in triglycerides can be predicted with each subsequent cisplatin in patients with excess body weight.

Obesity increases the risk of multiple disease states including hypertension, diabetes mellitus, and coronary artery disease (Polk, 2005). The comorbidities, frequently associated with obesity, result in the need for numerous medications to manage these conditions. Obesity alters the disposition of drugs in the body (pharmacokinetics), which should be considered when prescribing medications in this patient population. Failure to adjust doses in obesity may result either in therapeutic failure or increased toxicity.

Some importance during therapy is to diet. Diets high in refined carbohydrates, with carbohydrates accounting for more than 60% of the total energy intake, can increase triglyceride levels (American Heart Association (AHA), 2014, April 21). Of note is how the correlation is stronger for those with higher BMI (28+) and insulin resistance (more common among the overweight and obese patients) is a primary suspect cause of this phenomenon of carbohydrate-induced hypertriglyceridemia (Parks, 2002). Those with a body mass index (BMI) equal to or greater than 28 kg/m^2 experienced a 30% increase in TAG concentration, while those whose BMI was less than 28, experienced no change...These data demonstrate that certain characteristics (e.g., BMI) can make some individuals more sensitive with respect to lipid and lipoprotein changes when dietary CHO is increased. Such characteristics that have been identified from previous work in this field and include BMI, insulin sensitivity (Coulston, Hollenbeck, Swislocki & Reaven, 1989), concentration of TAG before the dietary change is made (Parks et. al., 2001), hormone replacement therapy (Kasim-Karakas, Almario, Mueller & Peterson, 2000), and genetic factors (Dreon, Fernstrom, Williams & Krauss, 2000). There is evidence that carbohydrate consumption causing a high glycemic index can cause insulin overproduction and increase triglyceride levels in women (Andrew Weil, 2003, September 22). Adverse changes associated with carbohydrate intake, including triglyceride levels,

are stronger risk factors for heart disease in women than in men (JAMA Internal Medicine, 2010, January 5).

A relatively small number of patients in each gender group can be considered as an important limitation of this study. There was no possibility to test the regression model for males and females separately. However, the patients' gender was controlled by the regression model as an independent variable. Another limitation is associated with evaluation of triglyceride changes as a difference between two measures. Evaluation of pharmacokinetics and changes in a longer time interval is a question for the further research.

Conclusion:

A comparison of female and male subsamples revealed no significant differences in measures regarding changes in triglycerides. Therefore, the study provides no evidence for differences in a toxic effect between sexes. The higher cisplatin dose and higher body fat mass are significant predictors for an increase in the triglyceride level. Considered to be among thecardiovascularrisk factors, increasing triglycerides are particularly important for oncology patients with overweight and cardiac co-morbidities.

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