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Standardization and Scoring of the Body Surface Area (BSA) Formulas for Calculation of the Doses of Anticancer Agents for Cancer Patients from the North-Western Nigeria

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Abstract

Background: Allometric scaling is an empirical examination of the relationship between the pharmacokinetic parameters and body size. Because of the importance of body surface area formulas for calculation of anticancer agents, there is need to standardize and score all the existing body surface area formulas with a view to obtaining the best and most efficient formula that can be adopted for use by our hospitals.

Methods: A total of 33 (10.3%) out of 319 presented to the Haematology Department of Usmanu Danfodiyo University Sokoto, Nigeria were diagnosed of Leukaemia and lymphoma. Cyclophosphamide, daunorubicin, vincristine, adriamyin and chlorambucil were used for the treatments. Eleven (11) of the affected 33 patients were randomly selected for calculation of their body surface areas using the formulas of DuBois, Boyd, Gehan and George, Haycock et al., Monsteller, Wang et al., Takashira and Fujimoto. The mean of the results obtained from each formula and for each individual was calculated and compared with all the results provided by the respective formulas and all the formulas scored.

Results: Wang et al. recorded the highest score 21 (21.2%) followed by DuBois 20(20.2%), this paper 18 (18.2%), Monsteller 18 (18.2%), Haycock et al. 14 (14.2%), Boyd 13 (13.1%), Gehan and George 13(13.1%), Takashira 4 (4.0%) and Fujimoto 3 (3.0%).

Conclusion: Wang et al. gives moderate effective anticancer doses and it is therefore recommended for the patients. It provides neither moderate doses of anticancer agents that may cause increased toxicity signs nor high risk of cancer remission.

Keywords: BSA; Anticancer agents; Leukaemia; Standardization; Body weight; Nigeria

Introduction

The safety of drug dosing has become a concern, even for drugs that produce therapeutic effects at doses far lower than those that cause toxicity. Errors in dose calculation of anticancer agents are even a greater concern because of high incidence of serious or life-threatening toxicity associated with many of them. Pharmacologically based or pharmaco-genetically based dosing may be far more rewarding than body surface area based dosing [1].

The DuBois formula, which is the western standard formula, is validated to a greater extent and its accuracy has been confirmed more than others, including the Fujimoto formula. Recommended is the use of the DuBois formula instead of Fujimoto formula in cancer chemotherapy and the standardization of this formula had been proposed in Japan [2]. There is a presumed narrow therapeutic index for most anticancer agents as shown in breast cancer [3,4], testicular cancer [5], lymphoma [6], and other cancers [2]. Selecting doses of anticancer agents to treat cancer patients can be a challenging decision for medical oncologists [2].

In 1916, DuBois and DuBois reported the BSA formula with direct measurements of nine subjects including a 36-years-old cretin with an underdeveloped physique, a 12-year-old boy, a tall thin adult male, and a short, obese adult female [7]. In 1978, Haycock et al. reported another formula based on measurements of 81 Caucasian, African American and Hispanic subjects [8]. In 1984, Martin et al. determined the BSA from 20 aged cadaver subjects by planimetry on paper tracings of dissected skin and compared the measured surface area and recommended continued use of the DuBois formula [9]. In 1987, Monstellar [10] modified the Gehan and George formula [11] and simplified it to enable the calculation using a pocket calculator. In 1992, Wang et al. measured the BSA with 60 pregnant women (34 to 40 week gestation) and 148 neonates [12]. Regardless of these highly varying statures, the DuBois formula and other western formulas adequately predicted the measured surface area and DuBois formula was finally recommended as the standard. The Fujimoto formula for adults is one of the most commonly used BSA formulas in Japan [2]. Cancer being a man-made fuelled by the excess of modern life as revealed by a study of ancient remains [13] requires a radical therapeutic approach that put into consideration the use of body surface area that would give moderate effective doses of anti-cancer agents.

Materials and Methods

A total of 319 patients were presented to the Department of

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Haematology, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria between January 2008 and December 2013. Patients with diagnosed cases of chronic myeloleukaemia, Non-Hodgekin lymphoma, chronic lymphocytic leukaemia, chronic myeloid lymphoma, Hodgekin disease, chronic myeloid leukaemia, chronic lymphoma, chronic lymphocytic leukaemia, acute leukaemia, Kaposi's sarcoma, chronic leukaemic lymphoma and chronic myeloid lymphoma were separated from other cases. The commonly used drugs for the treatment of the reported cases are cyclophosphamide, daunorubicin, vincristine, adriamycin and chlorambucil. The formulas used for the calculation of body surface areas for the anticancer agents are DuBois, Boyd, Gehan and George, Haycock et al., Monstellar, Wang et al., Takashira, Fujimoto and Schlich et al. [7,8,10-16] and this paper (Table 1). The rationale of the formula used in this paper was based on the principle of calculating the mean of the results (BSAs) obtained from each formula and for each individual. Then DuBois formula was used to determine the constant (i.e. $1.48 = KXH^{0.725} \times W^{0.425}$) where constant (K) is equal to 2.008. In essence our formula was developed from all the findings from all the formulas used for calculation of BSAs in this paper.

The mean of the result obtained from each formula was compared with all the results provided by the respective formulas. The mean body weight of five underweight and six normal weights of the patients were calculated. Analysis of variance (ANOVA) was used to analyse the data. Least significant difference (LSD) was used to detect the significant difference among the means of BSAs calculated from all the formulas. The body surface areas calculated from the formulas were also scored to enable us identify the formulas that can give same results for possible comparisons on precision, validity and reliability [17].

Results

Thirty three (10.3%) out of 319 patients presented to the hospital were diagnosed of white blood cells cancers. Five out of the eleven selected from the 33 patients recorded low body mass index whereas the remaining six recorded normal body weight (Table 2). The results obtained from the use of BSA formula adopted by Wang et al. for all the eleven patients were same with the results obtained by other formulas giving Wang et al. a total score of 21(21.2%). All the results obtained for patients serial numbers 2 – 11 using Wang et al. are same and correlated with those obtained by DuBois which scored 20 (20.2%). However the Monstellar scored (18.2%) with patients serial numbers 2 and 11 having same values of BSA from DuBois, Haycock et al, Wang et al. and our mean (this paper). Haycock et al. scored 14 (14.1%) with patients serial numbers 3 and 11 having same BSAs also with Monstellar, DuBois, Wang et al. and our mean. Gehan and George and Body formulas scored 13 each whereas Takashira and Fujimoto scored 4 and 3 respectively. Schlich formula scored 2 (2.0%). The BSA values using Schlich formula for the patients serial number 1(2.03), 2(1.91), 3(1.38), 4(1.23), 5(1.33), 6(1.27), 7(1.07), 8(1.08), 9(1.03), 10(1.02) and 11(1.29) respectively are significantly lower ($P<0.05$) than values obtained by other formulas. The BSA values for patient serial number 1 are same using Monstellar and Wang et al. Schlich formula recorded lowest values of BSA whereas Fujimoto recorded relatively lower BSA values. But Takashira relatively recorded high BSA values. But the mean BSA values of all the patients as obtained from Monstellar, DuBois, Haycock

S/No	Author	Year of publication	No. of Patients	Formula
1	Monsteller [10]	1987	Modified Gehan and George	$([H \times W]/3600^{1/2})$
2	DuBois [7]	1916	9	$2.0247 \times 10^{-1} \times H^{0.725} \times W^{0.425}$
3	Haycock et al. [8]	1978	81	$2.4265 \times 10^{-2} \times H^{0.42246} \times W^{0.51456}$
4	Gehan and George [11]	1970	401	$2.35 \times 10^{-2} \times H^{0.42246} \times W^{0.51456}$
5	Boyd [14]	1935	411	$3.207 \times 10^{-4} \times H^{0.3} \times W^{0.7285}$
6	Wang et al. [12]	1992	Modified DuBois	$7.184 \times 10^{-3} \times H^{0.725} \times W^{0.425}$
7	Takashira [15]	1925	Unknown	$7.241 \times 10^{-3} \times H^{0.725} \times W^{0.425}$
8	Fujimoto [15]	1968	201	$8.883 \times 10^{-3} \times H^{0.663} \times W^{0.444}$
9	Saganuwan and Ndakotsu [unpublished]	This paper	11-Modified DuBois	$2.008 \times 10^{-1} \times H^{0.725} \times W^{0.425}$

Table 1: Body surface area formulas.

S/No	Sex	Age	Body weight (kg)	Height (m)	Body Mass Index	Body Surface Area								
						Monsteller [10] (a)	DuBois and DuBois [7] (b)	Haycock et al. [8] (c)	Gehan and George [11] (d)	Boyd [14] (e)	Wang et al. [12] (f)	Takashira [15] (g)	Fujimoto [15] (h)	Mean (i)
1	M	70	78	1.9	21.61	2.05^{f}	2.12	2.02	2.03	2.01	2.05^{a}	2.07	1.99	2.04
2	F	21	72	1.85	21.04	1.92^{c}	1.95^{f}	1.92^{a}	1.93^{i}	1.91	1.95^{b}	1.96	1.89	1.93^{d}
3	F	37	51.3	1.58	20.55	1.50^{bcfi}	1.50^{acfi}	1.50^{abfi}	1.51^{e}	1.51^{d}	1.50^{abci}	1.52	1.46	1.50^{abcf}
4	M	14	48.0	1.48	21.91	1.40^{i}	1.39^{f}	1.41^{g}	1.42	1.43	1.39^{b}	1.41^{c}	1.36	1.40^{a}
5	F	45	46.5	1.59	18.39*	1.43^{c}	1.45^{f}	1.43^{a}	1.44^{ei}	1.44^{di}	1.45^{b}	1.46	1.41	1.44^{de}
6	M	14	44.8	1.55	18.65*	1.39^{i}	1.40^{def}	1.38	1.40^{bef}	1.40^{bdf}	1.40^{bde}	1.41	1.36	1.39^{a}
7	F	14	44.0	1.63	16.56*	1.44^{bf}	1.44^{af}	1.40^{ei}	1.42^{i}	1.40^{c}	1.44^{ab}	1.45	1.40^{ce}	1.42^{d}
8	M	15	35.5	1.46	16.65*	1.20^{ei}	1.21^{df}	1.19	1.21^{bf}	1.20^{ai}	1.21^{bd}	1.22	1.12	1.20^{ae}
9	M	12	31.4	1.46	14.73*	1.27	1.15^{f}	1.12^{h}	1.14	1.13	1.15^{b}	1.16^{i}	1.12^{c}	1.16^{g}
10	F	20	43.0	1.58	17.22	1.37^{e}	1.40^{f}	1.36	1.38^{i}	1.37^{a}	1.40^{b}	1.41	1.35	1.38^{d}
11	F	14	48.0	1.53	20.50	1.43^{bcfi}	1.43^{acfi}	1.43^{abfi}	1.44^{eg}	1.44^{dg}	1.43^{abci}	1.44^{de}	1.39	1.43^{abcf}
Mean	-	25.09	49.31	1.60	18.89	1.49**	1.49**	1.47***	1.47***	1.48****	1.49**	1.50	1.44	1.48****
SEM	-	5.53	5.96	0.04	0.92	0.07	0.08	0.08	0.08	0.07	0.08	0.08	0.08	0.08
Score	-	-	-	-	-	18	20	14	13	13	21	4	3	18

Keys: * = Underweight, - = Not applicable

Table 2: The Scoring of body surface area (BSA) formulas for calculation of doses of anticancer agents.

et al., Gehan and George, Boyd, Wang et al., Takashira and Fujimoto didn't differ significantly in comparison with our mean. Because of poorest performance of Schlich formula, it was not compared with the rest of the formulas (Table 2).

Tables 3-7 show the calculated doses of cyclophosphamide, daunorubicin, vincristine, doxorubicin and chlorambucil to be increased using Takashira formula and decreased using Fujimoto formula. The formulas of Haycock, Gehan and George provided moderate average BSA for calculated doses of the anticancer agents (Tables 3-7). However, Wang et al. produced the most moderate doses of the anticancer agents (Tables 3-7).

Discussion

The fact that 10.3% of the reported cases have white blood cells cancer means that cancer constitutes a significant problem among the people from the North Western Nigeria. The weights of eleven patients whose BSAs were calculated are either underweight or normal weight. So the cancer cases recorded among the patients may not be all attributable to overweight. The relative risks associated with excess weight vary. But generally, there is a strong connection between excess weight and cancer risk for a large number of tumor types [18]. There is a moderate positive association between processed meat consumption and mortality in particular due to cardiovascular diseases, and some forms of cancers [19]. In addition, cell proliferation, cell volume and or biomarkers of protein synthesis may predict response to drugs targeting cancer metabolism [20]. The fact that Wang et al. [12] had the highest score of the correlation of BSA values agrees with the report of Miller [1] indicating that body surface area correlates with basal metabolic rate and is proportional to blood volume. BSA is neither correlated with glomerular filtration rate nor associated with liver function [21,22]. Freireich et al. quantitatively compared toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and humans and discovered that it correlates very well with body surface area [23].

But the values of BSAs obtained from Dubois [7] are highly correlated with that of Wang et al. [12] suggesting interrelationship of the two formulas. But since the heights of the patients' serial numbers

S/No	Sex	Age	Body weight (kg)	Height (m)	Body Mass Index	Doses of oral cyclophosphamide (mg/m²)								
						Monsteller [10] (a)	DuBois and DuBois [7] (b)	Haycock et al. [8] (c)	Gehan and George [11] (d)	Boyd [14] (e)	Wang et al. [12] (f)	Takashira [15] (g)	Fujimoto [15] (h)	Mean (i)
1	M	70	78	1.9	21.61	205^{f}	212	202	203	201	205^{a}	207	99	204
2	F	21	72	1.85	21.04	92^{c}	95^{f}	92^{a}	93^{i}	91	95^{b}	96	89	93^{d}
3	F	37	51.3	1.58	20.55	50^{bcfi}	50^{acfi}	50^{abfi}	51^{e}	51^{d}	50^{abci}	52	46	50^{abcf}
4	M	14	48.0	1.48	21.91	40^{i}	39^{f}	41^{g}	42	43	39^{b}	41^{c}	36	40^{a}
5	F	45	46.5	1.59	18.39*	43^{c}	45^{f}	43^{a}	44^{ei}	44^{di}	45^{b}	46	41	44^{de}
6	M	14	44.8	1.55	18.65*	39^{i}	40^{def}	38	40^{bef}	40^{bdf}	40^{bde}	41	36	39^{a}
7	F	14	44.0	1.63	16.56*	44^{bf}	44^{af}	40^{ei}	42^{i}	40^{ci}	44^{ab}	45	40^{ce}	42^{d}
8	M	15	35.5	1.46	16.65*	20^{ei}	21^{df}	19	21^{bf}	20^{ai}	21^{bd}	22	12	20^{ae}
9	M	12	31.4	1.46	14.73*	27	15^{f}	12^{h}	14	13	15^{b}	16^{i}	12^{c}	16^{g}
10	F	20	43.0	1.58	17.22	37^{e}	40^{f}	36	38^{i}	37^{a}	40^{b}	41	35	38^{d}
11	F	14	48.0	1.53	20.50	43^{bcfi}	43^{acfi}	43^{abfi}	44^{eg}	44^{dg}	43^{abci}	44^{de}	39	43^{abcf}
Mean	-	25.09	49.31	1.60	18.89	49**	49**	47***	47***	48****	49**	50	44	48****
SEM	-	5.53	5.96	0.04	0.92	7	8	8	8	7	8	8	08	8
Score	-	-	-	-	-	18	20	14	13	13	21	4	3	18

Keys: * = Underweight, - = Not applicable

Table 3: Calculated oral doses of cyclophamide (100mg/m²) using various body surface area (BSA) formulas.

S/No	Sex	Age	Body weight (kg)	Height (m)	Body Mass Index	Doses of oral daunorubicin (mg/m²)								
						Monsteller [10] (a)	DuBois and DuBois [7] (b)	Haycock et al. [8] (c)	Gehan and George [11] (d)	Boyd [14] (e)	Wang et al. [12] (f)	Takashira [15] (g)	Fujimoto [15] (h)	Mean (i)
1	M	70	78	1.9	21.61	61.5^{f}	63.6	60.3	60.9	60.3	61.5^{a}	62.1	59.7	61.2
2	F	21	72	1.85	21.04	57.6^{c}	48.5^{f}	57.6^{a}	57.9^{i}	57.3	58.5^{b}	58.8	56.7	57.9^{d}
3	F	37	51.3	1.58	20.55	45^{bcfi}	45^{acfi}	45^{abfi}	45.3^{e}	45.3^{d}	45^{abci}	45.6	43.8	45^{abcf}
4	M	14	48.0	1.48	21.91	42^{i}	41.7^{f}	42.3^{g}	42.6	42.9	41.7^{b}	42.3^{c}	40.8	42^{a}
5	F	45	46.5	1.59	18.39*	42.9^{c}	43.5^{f}	42.9^{a}	43.2^{ei}	43.2^{di}	43.5^{b}	43.8	42.3	43.2^{de}
6	M	14	44.8	1.55	18.65*	41.7^{i}	42^{def}	41.4	42^{bef}	42^{bdf}	42^{bde}	42.3	40.8	41.7^{a}
7	F	14	44.0	1.63	16.56*	43.2^{bf}	43.2^{af}	42^{ei}	42.6^{i}	42^{ci}	43.2^{ab}	43.5	42^{ce}	42.6^{d}
8	M	15	35.5	1.46	16.65*	36^{ei}	36.3^{df}	35.7	36.3^{bf}	36^{ai}	36.3^{bd}	36.6	33.6	36^{ae}
9	M	12	31.4	1.46	14.73*	38.1	34.5^{f}	33.6^{h}	34.2	33.9	34.5^{b}	34.8^{i}	33.6^{c}	34.8^{g}
10	F	20	43.0	1.58	17.22	41.1^{e}	42^{f}	40.8	41.4^{i}	41.1^{a}	42^{b}	42.3	40.5	41.4^{d}
11	F	14	48.0	1.53	20.50	42.9^{bcfi}	42.9^{acfi}	42.9^{abfi}	43.2^{eg}	43.2^{dg}	42.9^{abci}	43.2^{de}	41.7	42.9^{abcf}
Mean	-	25.09	49.31	1.60	18.89	44.7**	44.7**	44.1***	44.1***	44.4****	44.7**	45.0	43.2	44.4****
SEM	-	5.53	5.96	0.04	0.92	2.1	2.4	2.4	2.4	2.1	2.4	2.4	2.4	2.4
Score	-	-	-	-	-	18	20	14	13	13	21	4	3	18

Keys: * = Underweight, - = Not applicable

Table 4: Calculated intravenous doses of daunorubicin (30mg/m²) using various body surface area (BSA) formulas.

S/No	Sex	Age	Body weight (kg)	Height (m)	Body Mass Index	Doses of oral vincristine (mg/m²)								
						Monsteller [10] (a)	DuBois and DuBois [7] (b)	Haycock et al. [8] (c)	Gehan and George [11] (d)	Boyd [14] (e)	Wang et al. [12] (f)	Takashira [15] (g)	Fujimoto [15] (h)	Mean (i)
1	M	70	78	1.9	21.61	2.87^{f}	2.96	2.82	2.84	2.81	2.87^{a}	2.89	2.78	2.85
2	F	21	72	1.85	21.04	2.68^{c}	2.73^{f}	2.68^{a}	2.7^{i}	2.67	2.73^{b}	2.74	2.64	2.7^{d}
3	F	37	51.3	1.58	20.55	2.1^{bcfi}	2.1^{acfi}	2.1^{abfi}	2.11^{e}	2.11^{d}	2.1^{abci}	2.12	2.04	2.1^{abcf}
4	M	14	48.0	1.48	21.91	1.96^{i}	1.94^{f}	1.97^{g}	1.98	2.0	1.94^{b}	1.97^{c}	1.90	1.96^{a}
5	F	45	46.5	1.59	18.39*	2.0^{c}	2.03^{f}	2.0^{a}	2.01^{ei}	2.0^{di}	2.03^{b}	2.04	1.97	2.0^{de}
6	M	14	44.8	1.55	18.65*	1.94^{i}	1.96^{def}	1.93	1.96^{bef}	1.96^{bdf}	1.96^{bde}	1.97	1.90	1.94^{a}
7	F	14	44.0	1.63	16.56*	2.01^{bf}	2.01^{af}	1.96^{ei}	1.68^{i}	1.96^{ci}	2.01^{ab}	2.03	1.96^{ce}	1.98^{d}
8	M	15	35.5	1.46	16.65*	1.68^{ei}	1.69^{df}	1.66	1.69^{bf}	1.68^{ai}	1.69^{bd}	1.70	1.56	1.68^{ae}
9	M	12	31.4	1.46	14.73*	1.77	1.61^{f}	1.56^{h}	1.59	1.58	1.61^{b}	1.62^{i}	1.56^{c}	1.62^{g}
10	F	20	43.0	1.58	17.22	1.91^{e}	1.96^{f}	1.90	1.93^{i}	1.91^{a}	1.96^{b}	1.98	1.82	1.93^{d}
11	F	14	48.0	1.53	20.50	2.06^{bcfi}	2.0^{acfi}	2.00^{abfi}	2.01^{eg}	2.01^{dg}	2.00^{abci}	2.01^{de}	1.94	2.00^{abcf}
Mean	-	25.09	49.31	1.60	18.89	2.08**	2.08**	2.05***	2.05***	2.07****	2.08**	2.10	2.01	2.07****
SEM	-	5.53	5.96	0.04	0.92	0.09	0.11	0.11	0.11	0.09	0.11	0.11	0.11	0.11
Score	-	-	-	-	-	18	20	14	13	13	21	4	3	18

Keys: * = Underweight, - = Not applicable

Table 5: Calculated oral doses of vincristine (1.4mg/m²) using various body surface area (BSA) formulas.

S/No	Sex	Age	Body weight (kg)	Height (m)	Body Mass Index	Doses of intravenous doxorubicin (mg/m²)								
						Monsteller [10] (a)	DuBois and DuBois [7] (b)	Haycock et al. [8] (c)	Gehan and George [11] (d)	Boyd [14] (e)	Wang et al. [12] (f)	Takashira [15] (g)	Fujimoto [15] (h)	Mean (i)
1	M	70	78	1.9	21.61	102.5^{f}	106	101	101.5	100.5	102.5^{a}	103.5	99.5	102
2	F	21	72	1.85	21.04	96^{c}	97.5^{f}	96^{a}	96.5^{i}	95.5	97.5^{b}	98	94.5	96.5^{d}
3	F	37	51.3	1.58	20.55	75^{bcfi}	75^{acfi}	75^{abfi}	75.5^{e}	75.5^{d}	75^{abci}	76.0	73.0	75.0^{abcf}
4	M	14	48.0	1.48	21.91	70^{i}	69.5^{f}	70.5^{g}	71.0	71.5	69.5^{b}	70.5^{c}	68.0	70^{a}
5	F	45	46.5	1.59	18.39*	71.5^{c}	72.5^{f}	71.5^{a}	72.0^{ei}	72.0^{di}	72.5^{b}	73.0	70.5	72.0^{de}
6	M	14	44.8	1.55	18.65*	69.5^{i}	70.0^{def}	69.0	70.0^{bef}	70.0^{bdf}	70.0^{bde}	70.5	68.0	69.5^{a}
7	F	14	44.0	1.63	16.56*	72.0^{bf}	72.0^{af}	70.0^{ei}	71.0^{i}	70.0^{ci}	72.0^{ab}	72.5	70.0^{ce}	71.0^{d}
8	M	15	35.5	1.46	16.65*	60.0^{ei}	60.5^{df}	59.5	60.5^{bf}	60.0^{ai}	60.5^{bd}	61.5	56.0	60.0^{ae}
9	M	12	31.4	1.46	14.73*	63.5	57.5^{f}	56.0^{h}	57.0	56.5	57.5^{b}	58.0^{i}	56.0^{c}	58.0^{g}
10	F	20	43.0	1.58	17.22	68.5^{e}	70.0^{f}	68.0	69.0^{i}	68.5^{a}	70.0^{b}	70.5	67.5	69.0^{d}
11	F	14	48.0	1.53	20.50	71.5^{bcfi}	71.5^{acfi}	71.5^{abfi}	72.0^{eg}	72.0^{dg}	71.5^{abci}	72.0^{de}	69.5	71.5^{abcf}
Mean	-	25.09	49.31	1.60	18.89	74.5**	74.5**	73.5***	73.5***	74.0****	74.5**	75.0	72.0	74.0****
SEM	-	5.53	5.96	0.04	0.92	3.5	4.0	4.0	4.0	3.5	4.0	4.0	4.0	4.0
Score	-	-	-	-	-	18	20	14	13	13	21	4	3	18

Keys: * = Underweight, - = Not applicable

Table 6: The recommended intravenous doses of do×orubicin (50mg/m²) using various body surface area (BSA) formulas.

3 – 11 were below 170cm, DuBois, Wang et al., Haycock et al. and Monstellar recorded many similar results. For a typical case where the height was 170 cm and the body mass index was 22 kg/m², the five western formulas and the Takashira formula calculations resulted in similar BSA products [16]. However, compared with the other formulas, only the Fujimoto formula underestimated BSA by about 3%. Therefore, using Fujimoto formula to dose the 33 patients may lead to under-dose of the anticancer agents. Our finding is in agreement with the report of Kouno et al. [2] indicating that the anticancer agents might be under dosed in Japanese patients when using the Fujimoto formula. The average BSA for Haycock et al. and Gehan and George is 1.47 ± 0.08 and for Boyd is 1.48 ± 0.007 which may likely have tendency for underestimation of anticancer agents (Tables 2-7). Compared to the Fujimoto formula, the Boyd, Gehand and George, Haycock et al. and Monstellar formulas have a tendency to overestimate the BSA of short and obese patients and to underestimate it for tall and thin patients. But the average BSA for Monstellar, DuBois and Wang et al. are 1.49 ± 0.07, 1.49 ± 0.08 and may be good for calculation of anticancer agents. Out of the three, Monstellar may be the best. But the fact that Fujimoto scored 1.44 ± 0.08 disagrees with the report of Kuono et al. indicating that the discrepancy between the Fujimoto and DuBois formulas was relatively smaller than the discrepancies between the Fujimoto formula and other western formulas. Prikel examined past studies and determined paediatric and adults' doses for Mercaptopurine, Methotrexate, Mechlorethamine, Triethylenethio-phosphamide and Actinomycin using DuBois formula [7] and the Meeh's formula [24] for animals and the results compared [25,26]. It was found that similar values for the doses per unit surface area were obtained for each agent. However BSA-based dose calculations has been criticized [27,28] because it failed to standardize the inter-patient variation in PK analysed for etoposide [29]; Calboplatin [6,30]; epirubicin [31,32], paclitaxel [21], cisplatin [30] and cyclophosphamide, Methotrexate, and 5-fluorouracil [33]. To enable us having a unified formula that can be used to calculate BSA of human and animals, there is need to know the length for each species of animals and the variation of body density during growth [34]. Pharmacologically based dosing or specific pharmaco-genetically base dosing may be far more rewarding than BSA dosing. Baker et al. have provided evidence that BSA dosing has very limited utility [35].

S/No	Sex	Age	Body weight (kg)	Height (m)	Body Mass Index	Doses of intravenous chlorambucil (mg/m²)								
						Monsteller [10] (a)	DuBois and DuBois [7] (b)	Haycock et al. [8] (c)	Gehan and George [11] (d)	Boyd [14] (e)	Wang et al. [12] (f)	Takashira [15] (g)	Fujimoto [15] (h)	Mean (i)
1	M	70	78	1.9	21.61	0.205^{f}	0.212	0.202	0.203	0.201	0.205^{a}	0.207	0.199	0.204
2	F	21	72	1.85	21.04	0.192^{c}	0.195^{f}	0.192^{a}	0.193^{i}	0.191	0.195^{b}	0.196	0.189	0.193^{d}
3	F	37	51.3	1.58	20.55	0.15^{bcfi}	0.15^{acfi}	0.15^{abfi}	0.151^{e}	0.151^{d}	0.15^{abci}	0.152	0.146	0.15^{abcf}
4	M	14	48.0	1.48	21.91	0.14^{i}	0.139^{f}	0.142^{g}	0.142	0.143	0.139^{b}	0.141^{c}	0.136	0.14^{a}
5	F	45	46.5	1.59	18.39*	0.143^{c}	0.145^{f}	0.143^{a}	0.144^{ei}	0.144^{di}	0.145^{b}	0.146	0.141	0.144^{de}
6	M	14	44.8	1.55	18.65*	0.139^{i}	0.14^{f}	0.138	0.14^{bef}	0.14^{bdf}	0.14^{bde}	0.141	0.136	0.139^{a}
7	F	14	44.0	1.63	16.56*	0.144^{bf}	0.144^{af}	0.14^{ei}	0.142^{i}	0.14^{ci}	0.144^{ab}	0.145	0.14^{ce}	0.142^{d}
8	M	15	35.5	1.46	16.65*	0.12^{ei}	0.121^{df}	0.119	0.121^{bf}	0.12^{ai}	0.121^{b}	0.122	0.112	0.12^{ae}
9	M	12	31.4	1.46	14.73*	0.127	0.115^{f}	0.112^{h}	0.114	0.113	0.115^{b}	0.116^{i}	0.112^{c}	0.116^{g}
10	F	20	43.0	1.58	17.22	0.137^{e}	0.14^{f}	0.136	0.138^{i}	0.137^{a}	0.14^{b}	0.141	0.135	0.138^{d}
11	F	14	48.0	1.53	20.50	0.143^{bcfi}	0.143^{acfi}	0.143^{abfi}	0.144^{eg}	0.144^{dg}	0.143^{abci}	0.144^{de}	0.139	0.143^{abcf}
Mean	-	25.09	49.31	1.60	18.89	0.149**	0.149**	0.147***	0.147***	0.148****	0.149**	0.15	0.144	0.148****
SEM	-	5.53	5.96	0.04	0.92	0.007	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008
Score	-	-	-	-	-	18	20	14	13	13	21	4	3	18

Keys: * = Underweight, - = Not applicable

Table 7: The calculated intravenous doses of chlorambucil (0.1mg/m²) using various body surface area (BSA) formulas.

This should serve as a challenge to find alternative dosing strategies for anticancer agents [1]. Indices of body measures are numerous for both humans and animals. Investigators used three approaches in measuring BSA: Coating, surface integration and triangulation. Dosing per unit of weight alone causes too large a dose for stronger medication. The principles of $BW^{1/1}$ for non-cancer endpoints and, at various times $BW^{2/3}$ or $BW^{3/4}$ for cancer endpoints to normalize dose across species may be adopted. But $BW^{3/4}$ has been promoted as default method to convert data between species. Dosimetric adjustment factor (DAF) = $(BW_a/BW_h)^{1/4}$ where "a" indicates animal, "h" indicates human and the ¼ exponent results from the application of $BW^{3/4}$ [36]. The exponent 2/3 has a highly significant correlation to body weight. The correlation coefficient amounts to + 0.71 and which disappears when the metabolic rate is divided by the ¾ power of bodyweight, which in turn is suitable unit of metabolic body size [37]. Alternative dosing strategies have been proposed in order to replace BSA dosing. Flat fixed dosing regimens have been suggested. But many hurdles will be probably had to be overcome before physicians will be willing to ban BSA dosing [38].

However, in the majority of investigational new drug applications, animal data are not available in sufficient detail to construct a scientifically valid, pharmacokinetic model whose aim is to accurately project the maximum recommended starting dose (MRSD) for first-in-human clinical trials of new molecular entities [39]. For many clinical purposes BSA is a better indicator of metabolic mass than body weight because it is less affected by abnormal adipose mass. But determining anticancer agents with a narrow therapeutic index using BSA has been criticized. For example the use of Takashira formula yielded a BSA of 1.50 $\pm$ 0.08 which is high and may lead to calculation of over doses of anticancer agents. But considering the standard error of mean for BSAs calculated using Monstellar and Takashira, the two formulas can be used for calculation of doses of anticancer agents for our patients (Tables 2-7). Because there is 4 – 10 fold variation in cytotoxic drug clearance between individuals due to differing activity of drug elimination processes related to genetic and environmental factors [40]. This can lead to significant overdosing and even more perniciously to under dosing and increase the risk of cancer recurrence. It is also distorting factor in phase I and phase II trials that may result in potentially helpful medications being prematurely rejected [41]. Schlich et al. proposed formula ($9.75482 \times 10^{-4} \times W^{0.46} \times H^{1.08}$) for women and ($5.79479 \times 10^{-4} \times W^{.038} \times H^{1.24}$) for men. The formula scored poor, less and does not conform to other formulas. Although a weight-based formula was proposed by Costeff [42] and recently validated for the paediatric age group that does not include a square root. It is [4W(kg) + 7]/[90 + Wkg] [43]. The fact that serial patients 1 and 2 recorded height of 190cm and 185cm respectively show that Nigerian man and woman can have long height. There was an average BSA of 1.73 m² for cancer patients from Europe [44]. BSA of 1.79 m² for adult patients in the UK, among them the average BSA for men was 1.91 m² and for women was 1.71 m². However, average BSA for neonate (0.25 m²), child of 2 years (0.5 m²), 9 years (1.07 m²), 10 years (1.14 m²), 12 – 13 years (1.33 m²), women (1.6 m²) and men (1.9 m²) have also been reported [45]. Excess weight is a clear risk factor for a number of cancers that are becoming prevalent in industrialized parts of the world. Aggressive prostate cancer risks are clearly increased in men that are in the overweight or obese categories [17].

A daily oral dose of cyclophosphamide 100 mg/m² for 14 days has been recommended for patients with lymphomas and chronic lymphocytic leukaemia. The recommended intravenous dose of daunorubim is 30 to 60 mg/m² daily for 3 days in treatment of Kaposis sarcoma. Adult patients with Hodgkin's disease or non-Hodgekin's lymphoma usually receive 1.4 mg/m² of Vincristin which seems to be tolerated better by children than by adults. The recommended dose of intravenous Doxorubicin (Adriamycin) is 50 to 75 mg/m² administered as a single rapid intravenous infusion that is repeated after 21 days. It is effective against malignant lymphomas. Chlorambucil is a standard agent for patient with chronic lymphocytic leukaemia at 0.1 to 0.2 µg/kg, given once daily and continued for 3 to 6 weeks [46]. Although, the Monsteller formula was adopted for use by the pharmacy and therapeutics of Cross Cancer Institute, Edmonton Alberta, Canada [47]. Reilly and Workman [48] and Gurney [21] suggested that the routine use of body surface area for dose calculation should be re-evaluated and that other methods of dose calculation should be investigated. Baker et al. have pondered scientific evidence that body surface area-based dosing has very limited utility [35].

Conclusion

BSA based dosing has failed to standardize the variation in PK for most anticancer agents, and individual dosing techniques are currently being investigated. However their utilities need to be confirmed and so

it is necessary to depend on the BSA-based calculation for determining the dose of most anticancer agents. But Wang et al. has been discovered to be the most suitable for white blood cells cancer patients from the North-Western Nigeria. It provides moderate doses of anticancer agents that may neither cause increased toxicity signs nor high risk of cancer remission.

Competing Interest

There is no competing interest, whatsoever between the authors and any other person, organization and Usmanu Danfodiyo University Teaching Hospital Sokoto, Nigeria.

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Author's contributions

Dr. S.A. Saganuwan collated and analysed the data. He also prepared and proof-read the manuscript. Dr. A.M. Ndakotsu is a consultant who attended to the patients. He diagnosed and treated the patients using different anticancer agents. He also proof-read the manuscript.

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