The relationship between fat free mass and toxicity of cytostatics in cancer patients

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INTRODUCTION & AIM

Body surface area (BSA) is used to calculate the dosage of cytostatic agents. As cytostatics are generally water soluble, the Fat Free Mass (FFM) would be a logical alternative to BSA for calculating the dosage of cytostatic agents.

We want to evaluate, if the dose of cytostatic agent[1]/FFM is related to toxicity.

[1] 5-Flourouracil, Oxaliplatin, Irinotecan, Capecitabine, Gemcitabine and Nab-Paclitaxel recieved as mono or combination therapy

METHOD

A single-center, observational and prospective study was performed on 69 colorectal and pancreatic cancer patients in systemic cytostatic treatment.

FFM was measured by bioimpedance spectroscopy (BIS-SOZO, ImpediMed) at the beginning of each treatment cycle for two-five cycles for two months. Toxicity outcomes were bone marrow depression, dose-limiting toxicity and hospitalization, patient-reported energy and protein intake (24-hour recall), general health, quality of life and selected side effects (PRO-CTCAE). Toxicity was measured for two months. Analysis was performed for the individual cytostatic agents and regimens.

RESULTS

No significant change in FFM was found after one or two months of treatment. Median (min-max) relative change in FFM after one and two months was -0.16 % (-11.5-13.0) and 1.48 % (-10.8-13.2) respectively. After adjusting for age and gender, a one unit increase in relative FFM was associated with reduced odds for hospitalization (OR=0.778 (95 % CI 0.617-0.982), p=0.034). Change in FFM was negatively correlated with length of hospitalization (r=-0.41 (95 % CI -0.655- -0.08), p=0.012). Other associations were non-significant after adjustment.

A one unit increase in baseline 5-Fluorouracil mg/FFM was related to a 2.04 % reduction in thrombocyte count/L from cycle 1 - 3 (95 % CI -3.65- -0.428, p=0.019) after adjusting. Other dose/FFM and toxicity estimates were non-significant or deemed inconclusive.
The correlation between BSA and FFM was r=0.846 (95 % CI 0.745-0.909), p<0.001.

Table 1. Change in fat free mass (FFM) and toxicity

	Change in FFM (kg) over 1 month from baseline (n=55)		**Change in FFM (kg) over 2 months from baseline (n=37)**	
	rho (95% CI)	OR (95% CI)	rho (95% CI)	OR (95% CI)
Neutropenia (<2,0 x 10^9/L) incidence	-0.24 (-0.47-0.04), p=0.085	-	-	-
Thrombocytopenia (<145 x 10^9/L) incidence	-	-	-	-
Dose-limiting toxicity incidence	-	-	-0.31 (-0.59-0-019), p=0.058	0.661 (0.425-1.027), p=0.066
Hospitalization incidence	-0.19 (-0.44-0.08), p=0.16	-	-0.40 (-0.65- -0.08), p=0.014*	0.778 (0617-0.982), p=0.034*
Duration of hospitalization (days)	-0.22 (-0.46-0.06), p=0.11	-	-0.41 (-0.66- -0.08), p=0.012*	-

Table 1 shows Spearman/Point Biseral correlation and logistic regression between change in FFM (kg) after one or two months and incidence/duration of toxicity during two months. Correlation analysis is limited to Mann-Whitney U-test estimates on groupings of toxicity incidence (yes/no) with p<0,4.

Table 2. Dose of cytostatics pr. fat free mass (FFM) at baseline and change in bone marrow cells

	Change in leucocyte count/L from baseline to cycle 2 (%)			**Change in thrombocyte count/L from baseline to cycle 3 (%)**		
	n	rho (95% CI)	B (95% CI)	n	rho (95% CI)	B (95% CI)
5-FU mg /FFM kg at 1. cycle	14	0.08 (-0.48-0.58), p=0.8	-	14	-0.62 (-0.88- -0.08), p=0.018*	-2.041 (-3.654- -0.428) p=0.019*
Oxaliplatin mg /FFM kg at 1. cycle	12	0.11 (-0.46-0.68) p=0.61	-	10	-0.46 (-0.86-0.27), p=0.18	-23.969 (-53.018-5.081), p=0.087
Irinotecan mg /FFM kg at 1. cycle	12	-0.18 (-0.69-0.44), p=0.58	-	12	-0.04 (-0.60-0.55), p=0.9	-
Capecitabine mg /FFM kg at 1. cycle	14	0.30 (-0.29-0.72) p=0.3	-	11	0.28 (-0.40-0.76), p=0.41	-

Table 2 shows Spearman correlation and linear regression between change in leucocyte and thrombocyte count in the cycle where they had the most noticeable change from baseline and the dose of cytostatic agent divided by FFM (mg/kg) at baseline. Regression analysis is limited to correlation with rho>0,4.

Table 3. Dose of cytostatics pr. fat free mass (FFM) at baseline and incidence of toxicity

	Neutropenia (<2,0 x 10^9/L), **incidence**		**Thrombocytopenia** (<145 x 10^9/L), **incidence**		**Dose-limiting toxicity, incidence**		**Hospitalization, incidence**	
	rho (95% CI)	OR (95% CI)	rho (95% CI)	OR (95% CI)	rho (95% CI)	OR (95% CI)	rho (95% CI)	OR (95% CI)
5-FU mg/FFM kg at baseline (n=32)	-0.24 (-0.55-0.12), p=0.18	-	0.22 (-0.15-0.53), p=0.23	-	-0.34 (-0.62-0.03), p=0.06	-	-0.28 (-0.57-0.09), p=0.13	-
5-FU mg/FFM kg at 1. cycle (n=14)	-	-	0.45 (-0.13-0.80), p=0.1	1.206 (0.969-1.502), p=0.093	-0.39 (-0.77-0.20), p=0.17	-	-	-
Oxaliplatin mg/FFM kg at baseline (n=29)	-	-	-0.20 (- 0.53-0.18), p=0.29	-	0.18 (-0.21-0.51), p=0.36	-	-	-
Oxaliplatin mg/FFM kg at 1. cycle (n=12)	0.36 (-0,29-0.78), p=0.26	-	-	-	-	-	-0.27 (-0.74-0.37), p=0.4	-
Irinotecan mg/FFM kg at baseline (n=25)	0.01 (-0.38-0.41), p=0.95	-	-	-	-	-	-	-
Irinotecan mg/FFM kg at 1. cycle (n=12)	0.49 (-0.16-0.84), p=0.11	128.77 (0.14-114362.16), p=0.16	-0.26 (-0.73-0.31), p=0.42	-	-0.31 (-0.76-0.34), p=0.33	-	-	-
Capecitabine mg/FFM kg at baseline (n=27)	-	-	-	-	-	-	-	-
Capecitabine mg/FFM kg at 1. cycle (n=14)	0.42 (-0.17-0.79), p=0.14	1.007 (0.997-1.017), p=0.18	0.25 (-0.31-0.70), p=0.38	-	-	-	-0.28 (-0.71-0.31), p=0.34	-
Gemcitabine mg/FFM kg at baseline (n=7)	-	-	0.87 (0.17-0.99), p=0.012*	-	-	-	-	-
Nab-paclitaxel mg/FFM kg at baseline (n=4)	-	-	0.89 (-0.71-0.999), p=0.11	-	-	-	-	-
Mann-Whitney U-test:	**Neutropenia (def.1/def.2/no)**		**Thrombocytopenia (yes/no)**		**Dose-limiting toxicity (yes/no)**		**Hospitalization (yes/no)**	
FFM kg/BSA (m^2)	p>0.4		p>0.4		p>0.4		p>0.4	
FFM kg/weight kg	p=0.24		p>0.4		p=0.33		p>0.4	

Table 3 shows Point-Biseral correlation and logistic regression between dose of cytostatic agent divided by FFM (mg/kg) at baseline or at the first cycle and incidence of toxicity during two months . Correlation analysis is limited to Mann-Whitney U-test estimates on groupings of toxicity incidence (yes/no) with p<0,4.The lower part of the table shows Mann-Whitney U-test estimates for FFM divided by BSA (kg/m^2) or FFM divided by weight (kg/kg) in groups of neutropenia (def. 1=<1,0x10^9/L, def. 2=<2,0x10^9/L and no=>2,0x10^9/L), thrombocytopenia (yes/no=</>145x10^9/L), dose-limiting toxicity (yes/no) and hospitalization (yes/no) during two months.

CONCLUSIONS

An association between FFM and cytostatic induced toxicity could not be proven. It is suspected that low statistical power and the reliability of estimates by BIS may have influenced the lack of a systematic correlation between FFM, and dose/FFM, and cytotoxicity in this study. Furthermore, the correlation between FFM and BSA was stronger than expected, which may have understated the role of FFM independent of BSA.

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