Evaluating the Association between BMI, Chemotherapy Toxicity, and Sarcopenia in Lung Cancer Patients

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Introduction

Body Mass Index (BMI) is a known adverse prognostic factor in many cancers, however the its contribution to progression and survival in patients with lung cancer is unknown. Traditionally, cytotoxic chemotherapy agents are dosed using body surface area wherein a cap exists to prevent toxicity in obese patients. However, previous studies have linked this reduction in obese individuals to poorer survival outcomes. Additionally, associations between skeletal muscle wasting (sarcopenia) and therapeutic toxicity have been reported, and sarcopenia may affect the distribution of chemotherapy agents. Host genetic factors may be modulating this effect.

The primary aim of this study was to evaluate a relationship between BMI and the severity, incidence, and outcomes of any occurring chemotherapeutic toxicities. In addition, we aim to investigate whether genetic variants (as measured by number of "risk alleles") that have been previously reported in relation to lean body mass may contribute to adverse events and progression in this cohort.

Methods

The cohort consisted of 198 patients with a non-small lung cancer diagnosis recruited at MSK between 2003 and 2008. Demographics and epidemiologic questionnaire data, and blood biospecimens for genetic and phenotypic studies were collected during the accrual period.

For this study, a thorough chart-review was conducted to determine diagnosis and interventional history (surgical, chemotherapeutic, and radiological). Additionally, clinical notes were reviewed for both hematological and non-hematological toxicity.

Patients were stratified by BMI: normal (<19.9), overweight (20.0 to 24.9), obese (>25.0). Toxicity was graded using NCI CTCAE version 4.

Candidate polymorphisms were selected based on literature on sarcopenia, lean mass, and appendicular mass. This was conducted using a PubMed search with keywords: sarcopenia, lean mass, muscle mass, BMI, and cancer.

Table 1: Patient characteristics

Weight Status	Normal (BMI <25)	Overweight (BMI 25-29.9)	Obese (BMI >30)
N (%)	103 (52.0%)	64 (32.3%)	31 (15.6%)
Age (years, avg)	66.6	65.8	69.7
Sex, (% Female)	74%	66%	58%
Race (% Caucasian)	77.7%	87.5%	80.6%
BMI (kg/m² avg)	21.9	27.0	34.4
Chemotherapy (% Received)	39 (37.9%)	17 (26.6%)	12 (41.9%)
Platinum-based Chemotherapy (% Received)	32 (82.1%)	8 (47.1%)	7 (58.3%)
Grade 3+ toxicity (% Experiencing)	9 (23.1%)	4 (23.5%)	4 (33.3%)

Table 2: Characteristics of candidate polymorphisms

SNP	Gene	Coordinates (GRCh38.7)	Genomic context	Major>minor alleles	MAF reported in Caucasian
rs12409277	PRDM16	chr1:2957600	Intergenic variant	T>C	0.208
rs4846048	MTHFR	chr1:11846252	3 prime UTR variant	A>G	0.301
rs2066470	MTHFR	chr1:11863057	Synonymous variant	C>T	0.1239
rs3737964	MTHFR	chr1:11867044	Intronic	G>A	0.283
rs491785	SLC25A24	chr1:108724693	Intronic	A>G	0.367
rs41526344	CNTN4	chr3:2985142	Intronic	C>T	0.092
rs1997623	CAV1	chr7:116165360	Synonymous variant	C>A	0.083-0.1
rs3807987	CAV1	chr7:116179834	Intronic	G>A	0.075
rs12672038	CAV1	chr7:116187106	Intronic	G>A	0.0845
rs3757733	CAV1	chr7:116193729	Intronic	T>A	0.2455
rs7804372	CAV1	chr7:116194228	Intronic	T>A	0.27
rs3807992	CAV1	chr7:116197245	Intronic	G>A	0.283
rs16892496	TRHR	chr8:110109851	Intronic	A>C	0.327
rs7832552	TRHR	chr8:110115676	Intronic	C>T	0.327
rs4751240	DOCK1	chr10:129136409	Intronic	G>A	0.58
rs2507838	GLYAT	chr11:58472799	Intronic	C>A	0.0354
rs7116722	GLYAT	chr11:58506899	Intergenic variant	C>A	0.0354
rs11826261	GLYAT	chr11:58515163	Downstream gene variant	C>T	0.04237

Results

- Obese patients received chemotherapy more frequently than both normal and overweight patients (41.9% vs 37.9% and 26.6%)
- Overweight and obese patients received platinum-based therapy half as much as those that are normal weight (58.3% and 47.1% vs 82.1%) (Table 1)
- Obese individuals experienced grade 3+ toxicities at a higher rate than both normal and overweight (33.3% vs 23% and 23.5% respectively)
- Literature review of sarcopenia and BMI yielded 8 genes with a total of 18 candidate SNPs (Table 2)
- Assays were designed to accommodate the candidate SNPs in two multiplex wells; one candidate SNP was replaced by a SNP in perfect linkage disequilibrium (rs xxxx for rsxxxx)

Next steps and future directions

- Further statistical analysis will be completed to assess the frequency of toxicities (gastrointestinal, pulmonary, and neurological, among others)
- Hematological toxicity will be assessed in a very similar fashion
- Genotyping assays will be performed to fine tune experimental conditions and then complete genotyping in the participants' germline DNA samples
- Our demographic, epidemiologic, clinical, and genetic data will be further analyzed in relation to toxicity and outcomes within the International Lung Cancer Consortia (ILCCO)

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