TOXICITY AND RELATIVE DOSE INTENSITY (RDI) OF FOLFOX 6 CHEMOTHERAPY IN PATIENTS, OF DIFFERING BODY MASS INDEX, TREATED FOR ADJUVANT AND METASTATIC COLORECTAL CANCER

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Background

Obesity is an established risk factor for developing colorectal cancer.[1] Although adiposity has been a recognised risk factor it's effect on treatment success and prevalence of treatment associated toxicities remains unclear. Some studies have found no association between obesity and any increase in chemotherapy related toxicity[2] and significantly lower rates of severe toxicity in overweight patients.[3] It is common practice for clinicians to cap the body surface area at $2m^2$ for obese individuals. Authors suggest that obese patients may be receiving sub-therapeutic doses of chemotherapy due to the association of less severe toxicity.[4,5]

Objective

To investigate the difference in percentage relative dose intensity (%RDI) and treatment induced toxicity between patients with normal BMI and overweight patients, treated with FOLFOX (see Table 1).

Chemotherapy Agent	Administration	Day
Calcium Leucovorin $400mg/m^2$	IV infusion in 500ml Dextrose 5% over 2 hours	1,15
Oxaliplatin $85mg/m^2$	IV Infusion in 500ml Dextrose 5% over 2 hours	1,15
Fluorouracil $400mg/m^2$	Slow IV push into the side arm of a fast running NaCl 0.9% drip	1,15
Fluorouracil $2,400mg/m^2$	IV infusion in 100ml NaCl 0.9% over 46 hours	1,15

Table 1:FOLFOX 6 Regimen

Method

• Patients who received FOLFOX were identified through pharmacy dispensing records.

• BMI classification was determined by weight at cycle 1 of treatment.

• Information on doses and toxicities was gathered retrospectively from electronic medical records and medical notes.

• The statistical solutions software package, nQuery (version 7.0), was used to calculate the sample size (n=17).

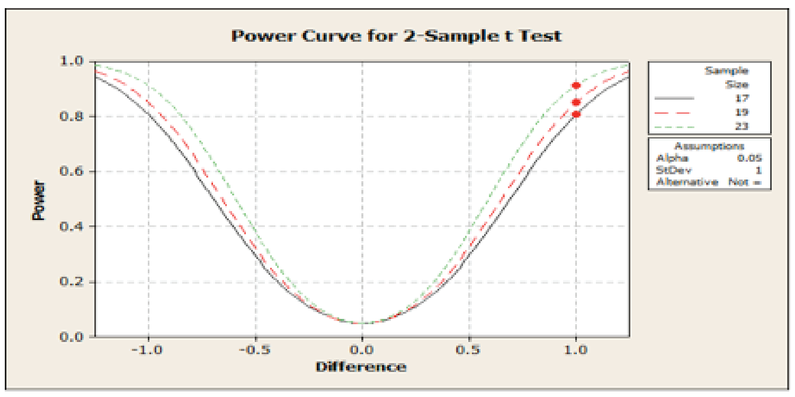

Figure 1: nQuery (version 7.0) software for sample size calculation.

The primary outcome measures were:

(1) Toxicity: Incidence and severity. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used to grade the severity of each toxicity.
(2) The percentage RDI. This was calculated using the following formula:

$$\%RDI = \frac{\text{Delivered Dose Intensity} \times 100}{\text{Standard Dose Intensity}}$$

• RDI is the relationship between the actual dose and duration of the delivered chemotherapy to the intended dose and duration of the standard chemotherapy regimen.

• All data collected was entered directly into Excel® 2007 and then transferred over to the statistical package, SPSS® (version 17).

• Statistics were analyzed using a power of 80% and significance level of 5%.

Results

• Patients with severe toxicities (CTCAE grade ≥ 3) had their dose reduced to prevent such toxicity recurring.

• CTCAE grade ≥ 3 were prevalent in 65% of normal BMI and 41% of overweight patients. Subsequent dose reductions occurred in 65% of the normal BMI and 53% of overweight patients.

• The incidence of fatigue was significantly higher in patients with a normal BMI, (p = 0.016), but there was no significant difference in other incidence of toxicities or the rate of hospital admissions due to toxicity.

Group	Grade 1	Grade 2	Grade 3	Grade 4
Overweight (n=17)	5 (29.4%)	2 (11.8%)	6 (35.2%)	1 (5.9%)
Normal BMI (n=17)	2 (11.8%)	2 (11.8%)	10 (58.8%)	1 (5.9%)

Table 2:The number of patients and % within each group who experienced each grade of toxicity

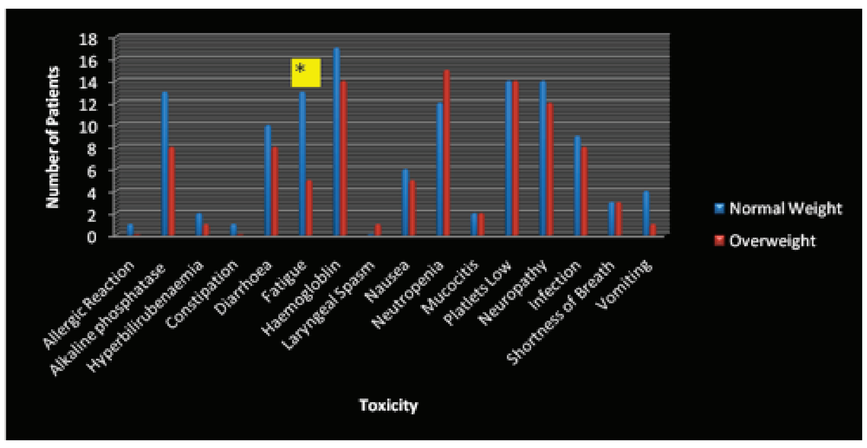

Figure 2:Incidence of toxicity between the normal BMI and overweight group

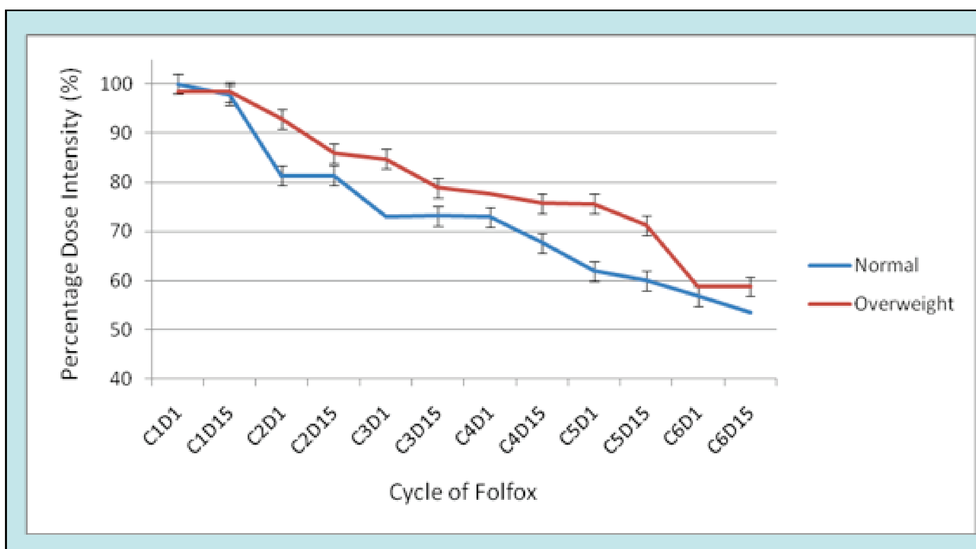

Figure 3: Dose reductions across the treatment cycles, error bars represent where a dose delay occurred.

• Patients of normal BMI received higher dose intensity at treatment initiation (as some patients in the overweight group had their BSA capped at $2m^2$) but received lower dose intensity for the remaining cycles compared to overweight patients.

• Overall the average %RDI of FOLFOX was 64.78% (normal BMI group: 18.5kg/m² to 25kg/m²) and 67.05% (overweight group: BMI >25kg/m²).

Discussion

Meyerhardt et al. found that with increasing BMI, patients experienced lower rates of grade ≥ 3 toxicity.[2] In this study the researcher found a similar result whereby the grade ≥ 3 toxicities in the overweight group were n= 7 (41%) and in the normal weight group were n=11 (65%).

Leonardo Lami et al. found that dose reductions occurred in thirteen (n=13, 23.2%) patients.[7] In this study nine (n=9, 53%) of the overweight group and eleven patients (n=11, 65%) of the normal BMI group, had dose reductions due to toxicity.

The overall low %RDI seen in both groups was a surprising result from this study. The presence of 41% metastatic patients in the normal BMI group and 29% metastatic patients in the overweight group influenced the lower dose intensities as it is considered more acceptable to dose reduce/delay in metastatic rather than in adjuvant disease.

The principal investigator found that only three patients had a dose intensity of <100% at initiation of treatment due to a capping of BSA at $2m^2$. If the sample of overweight patients had included more obese individuals in the cohort, this figure may have been higher and resulted in a significant difference in %RDI between the two groups.

Conclusion

The overweight group experienced less dose reductions than the normal BMI group indicating that they may be capable of tolerating doses based on actual body weight rather than capping the body surface area. The low %RDI received by both study groups may highlight a need to gain better control of toxicities. Future studies could investigate the impact of pharmacist counseling on supportive medication, with the aim of improving %RDI, particularly in adjuvant treatment.

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