Halting severe chemotherapy toxicity and improving patient outcomes in cancer treatment.

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SUMMARY

In cancer treatment, there is a narrow therapeutic window with chemotherapy agents. The most common reason for chemotherapy dose reduction is neutropenia resulting in impaired survival. Chemotherapy dosage is calculated based on body surface area, with no adjustment recommendation for a patient's albumin level even though chemotherapy medications are highly protein-bound. The insight gained by mathematical modeling suggests an altered free/bound drug ratio in patients with low albumin results in severe side effects. Furthermore, mathematical modeling also reveals impaired survival in dose-reduced chemotherapy patients may be from decreased bound drug levels while free drug levels remain unchanged. Restoring the free/bound drug ratio by correcting a patient's albumin deficit will reduce chemotherapy side effects and improve patient outcomes. Finally, enhanced chemotherapy treatment is possible by capping the free drug level and maximizing the bound drug level. The mathematical model predicts the following chemotherapy medications will have altered free/bound drug ratio in patients with low albumin: cisplatin, oxaliplatin, doxorubicin, epirubicin, idarubicin, paclitaxel, eribulin, etoposide, vinorelbine, bendamustine, chlorambucil, and pemetrexed.

INTRODUCTION

It is unknown what predisposing factors cause severe toxicity in chemotherapy patients, with some studies revealing the incidence of serious adverse effects occurring after chemotherapy affecting up to 44.5% of patients.[1] A study in advanced breast and ovarian cancer has shown 48.7% of patients require dose reduction because of severe side effects.[2] Chemotherapy dosage is calculated based on body surface area(BSA) to reduce medication variability in therapeutic and toxic effects. However, there is no adjustment recommendation in chemotherapy dose for a patient's albumin level even though chemotherapy medications are highly protein-bound. It is assumed in chemotherapy treatment that linear protein binding persists throughout the range of serum albumin levels.[3] A patient's albumin level may play a predominant role in chemotherapy toxicity since free drug levels can be dramatically higher than expected from total drug levels, especially for highly protein-bound drugs. [3] Thus, patients may experience drug toxicity even when total drug levels are within the therapeutic range.[3,4,5] There is evidence in patients treated with cisplatin that the risk factor for nephrotoxicity results in high peak plasma-free platinum concentrations.[6] In patients with hypoalbuminemia treated with medication the lower the albumin level the risk of side-effects is increased.[7] There are limited studies investigating the relationship between toxicity and free and bound drugs levels in chemotherapy treatment. The distribution characteristics of free and bound drugs are different. The free drug is widely distributed in the body resulting in severe side effects as the free drug reaches high levels. The bound drug limited to serum has fewer side effects, such as seen with Abraxane, acting as a carrier molecule that delivers the medication to metabolically active cells.[8,9] The major problem with chemotherapy treatment in cancer is drug toxicity represented by elevated free drug level.

Cisplatin and doxorubicin are common chemotherapy medications used to treat many types of cancer. Chemotherapy-related severe toxicity for both cisplatin and doxorubicin is neutropenia.[10] Other side effects reported with cisplatin treatment are nephrotoxicity, neurotoxicity, and ototoxicity.[10] The main side-effect, besides neutropenia with doxorubicin treatment, is cardiotoxicity.[10] Survival curves reports have shown chemotherapy dose reduction often results in dose reduction causing decreased patient survival.[11,12] In many studies, dose reduction of chemotherapy of more than 85% results in a decrease in survival.[11,12]

A mathematical model of chemotherapy dosing offers further insight into understanding how albumin levels alter the free and bound drug levels leading to an increased risk for severe chemotherapy toxicity. In this paper chemotherapy dosage is model by mathematical equations coupled with physiological parameters for total albumin and volume of distribution to determine free and bound drug levels. The total albumin does not scale with actual body weight but instead correlates with ideal body weight and lean body weight. A patient's actual body weight correlates with the volume of distribution. The model reveals patient physiological parameters and drug-specific characteristics that are important considerations for patients' chemotherapy treatment regime.

RESULTS

Figure 1a and 1b represent free drug levels over BMI for doxorubicin and cisplatin, respectively.

Figure 2a and 2b doxorubicin and cisplatin BSA dosing over albumin levels 25- 45g/L.

Figure 3a and 3b Capped free drug level dosing over albumin levels 25-45g/lLfor doxorubicin and cisplatin, respectively.

Figure 4 Image of a representative survival dose reduction curve graph superimposed over chemotherapy dose reduction by capped free drug level.

METHODS

Table 6 BMI reference range for hypoalbuminemia in obesity.

Table 7 Albumin correction

DISCUSSION

It is difficult to determine which patients will suffer from severe toxicity such as neutropenia before chemotherapy treatment. Mathematical modeling reveals patients with low albumin levels have dramatically altered free/bound drug ratios. The ratio change in drug levels leads to an excessive free drug level widely distributed to all tissues. Exposure of tissues to these increased free drug levels causes severe side effects. Conversely, diminished bound drug levels in patients with low albumin impact survival. The new insight gained by mathematical modeling suggests capping the free drug level and maximizing the bound drug level will refine chemotherapy treatment making it more effective and less toxic.

Many studies reveal albumin binding to medication is concentration-independent(linear protein binding), with drug levels increasing as the fraction unbound remains constant. In patients with normal albumin levels, a large percentage of the chemotherapy drug is bound to albumin with a small percentage as free drug. The high incidence of severe side-effects in hypoalbuminemia patients indicates non-linear protein binding plays a role in severe chemotherapy side-effects. A rapid rise in free drug levels occurs in non-linear protein binding once albumin binding sites become saturated increasing the fraction unbound. As revealed by phenytoin, non-linear protein binding occurs with an increase from 10% to 50% fraction unbound in a patient with low albumin.[4] In this way, albumin drug binding is analogous to a buffer solution at saturation with a dramatic rise in pH resulting from a small additional amount of acid or base. Phenytoin has similar protein binding and volume of distribution as cisplatin suggesting the cisplatin free/bound drug ratio is altered in patients with low albumin.[9] Further signs of the similarity between phenytoin and cisplatin is drug toxicity in patients with low albumin, suggesting non linear protein binding.[4,12] Studies have shown chemotherapy treated patients with low albumin levels less than 36g/L were associated with a higher risk of grade 3+ chemotherapy toxicity.[13,14] Thus, patients with low albumin who receive chemotherapy treament should raise the same concern of overdose as patient with phenytoin.

There are inconsistencies between doxorubicin and cisplatin dosing recommendations for obesity in the literature. Doxorubicin uses actual body weight for BSA dosing,[14] whereas the cisplatin dose is limited to 2.0m^2/mg BSA.15 The mathematical model using BSA dosing over various BMIs reveals the basis for restricting the cisplatin dose to 2.0m^2/mg BSA. For patients with a BMI of 50, the free drug level of cisplatin increased to 2.5x normal, in contrast to doxorubicin with an increased 1.54x normal (Figure 1a and b). The literature agrees with the mathematical model with actual body weight dosing for doxorubicin and capping the cisplatin dose at 2.0m^2/mg BSA to reduce toxicity.14,15 Doxorubicin has substantially less toxicity than cisplatin because of decreased protein binding of 75% and the large volume of distribution acting to dilute the free drug level. Cisplatin is highly bound to albumin at 90% and has a lower volume of distribution resulting in a higher free drug level and more toxicity than doxorubicin. In another paper, there is no evidence to show obese patients receiving chemotherapy experience increased toxicity with actual body weight BSA dosing.[16] In this paper, busulfan, cyclophosphamide, and cyclosporin are not bound to albumin, and methotrexate is minimally bound to albumin suggesting the total drug level closely represents the free level. These results show that high protein binding chemotherapy medications may make patients with low albumin vulnerable to drug toxicity because of an altered free-bound drug ratio. Shem-Tov et al. emphasize the lack of a standard of practice for dosing chemotherapy in obesity.[17] Taking the albumin binding characteristics of chemotherapy medications into consideration can help determine the appropriate dosing method for obese patients. Dose adjustment for highly albumin-bound chemotherapy medications are IBW and LBW, and medications not highly albumin-bound ABW.

There are two circumstances in chemotherapy treatment where a patient's low albumin level is problematic. One patient with low albumin who receives BSA-dosed chemotherapy has increased side effects because of high free drug levels. The other is dose-reduced chemotherapy resulting in decreased bound drug reducing survival. These circumstances reveal the dilemma in chemotherapy between the quality of life and survival where dose reduction reduces toxicity at the cost of survival.

Mathematical modeling BSA dosing of cisplatin and doxorubicin over varying albumin levels reveals chemotherapy medications differ in the factor of free drug levels rises. A considerable difference in the free drug level is shown between cisplatin and doxorubicin at 40g/L albumin at 2.0 times and 1.3 times, respectively (Figure 2a and b). Mathematical modeling for patients with albumin at 25g/L shows a dramatic rise in free drug levels of 2.32 to 4.8 times the normal free drug levels for doxorubicin and cisplatin, respectively (Figure 2a and b). In a paper by Dotan et al., an albumin level less than 36g/L had a higher risk of grade 3+ chemotherapy toxicity.[13] The graphs reveal as albumin levels decline, the factor rise in the free drug level increases resulting in a worsening degree of toxicity. The main reason for dose reduction in patients is neutropenia, this may occur because of high free drug levels in hypoalbuminemia.

Dosing chemotherapy with the concept of capping the free drug level over decreasing albumin levels may reflect the free and bound drug levels seen in patients who undergo dose-reduction chemotherapy. Capped free drug level dosing of chemotherapy for both cisplatin and doxorubicin results in decreased bound drug level compared with non-dose reduced patients or patients at 45g/L albumin (Figure 3a and b). In studies, patients who have received dose-reduced chemotherapy because of previous side effects can complete therapy similar to non dose-reduced patients.[11,12] Unfortunately, patients who have received dose-reduced chemotherapy are found to have decreased survival compared to non-dose reduced patients, suggesting a decrease in bound drug level may be to blame.[11,12]

A decrease in cancer survival with chemotherapy treatment revealed by dose reduction survival curve data may be related to a decrease in the bound drug level. Superimposing the cisplatin dose reduction mathematical model over chemotherapy survival curves reveals a correlation in survival with a drop in the bound drug level (Figure 4). The differene in bound drug level between no dose reduction and dose reduction at albumin 25g/L for doxorubicin and cisplatin was a decrease of 44.6% and 55% of normal, respectively. Thus, correcting the albumin deficit in cancer patients will restore the free and bound drug levels to those seen in non-reduced chemotherapy patients. In a study by Wang et al., patients with albumin less than 30g/L were infused with 30 grams of albumin before chemotherapy had reduced toxic symptoms.[19] A concern with the Wang et al. paper is the lack of albumin used. For example, a 75kg patient with albumin of 30g/L would need around 100grams of albumin to restore the patient to normal levels before chemotherapy treatment. The objective of an albumin infusion is to correct the free/bound drug ratio so it falls within the therapeutic window, where linear protein binding occurs, as oppose to non-linear protein binding. Correcting a patient's albumin deficit before chemotherapy treatment will help resolve the dilemma of quality of life versus survival. Reducing hospitalizations as a result of neutropenia prevention can have a significant reduction in medical care costs. In 2012 the cost of chemotherapy-induced neutropenia in the U. S was suggested at 2.3 billion.

Albumin-bound medications are under investigation to decrease the side effects of chemotherapy. Both cisplatin and doxorubicin have formulations developed that utilize albumin as a carrier molecule. In current studies, albumin-based nanoparticles deliver doxorubicin in breast cancer treatment. The albumin-bound complex of cisplatin is currently under further investigation.[20] Abraxane, an albumin-bound medication of paclitaxel, is used to treat many types of cancer.[7,8] In studies, nab-paclitaxel (albumin-bound) had improved event-free survival benefits but had no difference in survival compared to solvent-based paclitaxel.[7,8] Abraxane, Nab-paclitaxel, lack of improvement in patient survival might be due to the absence of free drug. These results may indicate the importance of the free drug working synergistically with the bound drug to improve survival.

Changing chemotherapy dosing from BSA to dosing based on free and bound drug levels will prevent toxicity and improve patient outcomes in cancer treatment. The mathematical modeling developed here predicts free and bound drug levels based on the specific chemotherapy medication and patient-specific characteristics. Enhanced chemotherapy treatment may be possible by capping the free drug level and maximizing the bound drug level allowing for more aggressive cancer treatment.

The mathematical model predicts the following: the difference in toxicity seen between two chemotherapy medications, the degree of toxicity associated with decreasing albumin, the importance of bound drug in survival, enhanced chemotherapy dosing, and reveals several other chemotherapy agents with high plasma protein binding. The underlying prediction is an increase in the fraction unbound of the drug will occur in a patient with hypoalbuminemia. The mathematical model confirmation is possible by measuring free and bound drug levels in chemotherapy patients with various albumin levels. Finally, a randomized double-blinded control trial of albumin supplementation versus no supplementation in hypoalbuminemia patients can reveal the differences in toxicity and survival.

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Table 1. Patient characteristics

BMI	25	30	35	40	45	50
Weight (kg)	81	97	114	130	146	162
Adjusted wt (kg)	75(IBW)	75(IBW)	75(IBW)	78.5(LBW)	82.5(LBW)	85.9(LBW)
BSAm^2(180cm)	2.01	2.17	2.32	2.45	2.58	2.69

Table 2. Doxorubicin free level with BSA dosing and adjusted weight total albumin

BMI	25	30	35	40	45	50
BSA dosing 75mg/ m^2 (µmol/mg)	278/151	300/163	320/174	339/184	357/194	372/202
Vd (1214L/m^2)	2440	2634	2816	2974	3132	3266
Total free amount µmol	79	101	121	133	138	144
Free level (µmol/L)	0.032	0.038	0.043	0.044	0.044	0.044
Factor over normal. (0.0284µmol/L)	1.12	1.34	1.51	1.54	1.54	1.54

Table 3. Cisplatin free level with BSA dosing and adjusted weight total albumin

BMI	25	30	35	40	45	50
BSA dosing 100mg/m^2 (µmol/mg)	670/201	723/217	773/232	817/245	860/258	897/269
Vd 12L/m^2 (L)	24.12	26.04	27.84	29.4	30.96	32.28
Total free amount µmol	88	141	191	208	220	230
Free level (µmol/L)	3.65	5.41	6.86	7.08	7.11	7.13
Factor over ideal body weight 75kg (2.78 µmol/L)	1.31	1.94	2.47	2.54	2.56	2.56

Table 4a. Estimated doxorubicin free drug level with dose of 75mg/m^2 (146mg (266µmol)) with BSA 1.94m^2 (180cm at 75kg) result in a total level of 0.1127 µmol/L over albumin 25-45g/L

Albumin g/L	45	40	35	30	25
Free drug total amount(µmols)	67	89	111	133	155.4
Free drug level (µmol/L)	0.0284	0.0380	0.0471	0.0564	0.0660
Fraction unbound	0.25	0.33	0.42	0.50	0.59
Bound drug level (µmol/L)	0.0845	0.0751	0.0660	0.0564	0.0470
Precent albumin binding %	75	67	58	50	41
Free/Bound ratio	0.34	0.51	0.72	1.0	1.4
Factor over normal free level	1	1.34	1.66	1.99	2.32

Table 4b. Estimated cisplatin free drug level with dose of 100mg/m^2 or194mg (646µmol) with BSA 1.94m^2 (180cm at 75kg) over albumin 25-45g/L

Albumin g/L	45	40	35	30	25
Free drug total amount(µmols)	64.66	130	194	259	323
Free drug level (µmol/L)	2.78	5.58	8.33	11.13	13.83
Fraction unbound	0.1	0.2	0.3	0.40	0.48
Bound drug level (µmol/L)	24.96	22.16	19.37	16.62	13.92
Precent albumin binding %	90	80	70	60	52
Free/Bound ratio	0.11	0.25	0.43	0.67	0.99
Factor over normal free level dose	1	2.0	2.99	4.00	4.81

Table 5a. Estimated doxorubicin bound drug level with dose reduction capped at free level of 0.0284µmol/L for patients with low albumin

Albumin g/L	45	40	35	30	25
Dose with free drug level capped at 0.0284µmol/L (µmol/mg)	266/146	243/132	221/120	199/108	177/96
Fraction unbound	0.25	0.28	0.30	0.33	0.38
Bound drug level after dose reduction (µmol/L)	0.0845	0.0751	0.0660	0.0564	0.0470
Precent albumin binding %	75	72	70	67	62
Free/Bound ratio	0.33	0.37	0.43	0.50	0.60
Total level (µmol/L)	0.113	0.103	0.094	0.084	0.075

Table 5b. Estimated cisplatin bound drug level with dose reduction capped at free level of 2.79 µmol/L for patients with low albumin

Albumin g/L	45	40	35	30	25
Dose with free drug level capped at 2.79µmol/L (µmol/mg)	646/194	581/174	516/154	451/135	387/116
Fraction unbound	0.1	0.11	0.125	0.144	0.17
Bound drug level after dose reduction (µmol/L)	24.96	22.16	19.37	16.62	13.92
Precent albumin binding %	90	89	88	86	83
Free/Bound ratio	0.11	0.125	0.144	0.17	0.2
Total level (µmol/L)	27.75	24.96	22.16	19.37	16.62

Table 6. BMI albumin reference range for hypoalbuminemia

BMI	25	30	35	40	45	50
BSA	2.01	2.17	2.32	2.45	2.58	2.69
Total albumin (g)	337(IBW)	337(IBW)	337(IBW)	337(IBW)	351(LBW)	366(LBW)
Vd 3.87L/m^2 (L)	7.78	8.40	8.99	9.48	9.98	10.4
Normal estimated albumin (g/L)	43.0	40.1	37.0	35.5	35.2	35.1

Table 7. Albumin deficit correction for patient of BMI 25

Albumin level g/L	45	40	35	30	25
Total albumin (g)	337	299	262	225	187
Albumin deficit correction (g)	0	38	75	112	150

Tabe 8. Chemotherapy dose, percent protein binding and albumin-drug binding capacity.

Drug	Dose (mg/m^2)	Percent protein binding/unbound[11]	Albumin-drug binding capacity (μmol/g)	Volume of distribution
Cisplatin	100	90%/10%	1.73	11-12 L/m^2
Oxaliplatin	130	90%/10%	1.67	440 L
Doxorubicin	75	75%/25%	0.59	809-1214 L/m^2
Epirubicin	120	77%/33%	0.96	2-27 L/kg
Idarubicin	12	97%/3%	0.129	1500 L/m^2
Paclitaxel	175	89-98%/11-2%	1.18	227-688 L/m^2
Eribulin	1.4	49-65%/51-35%	0.0052	43-114 L/m^2
Etoposide	100	94-98%/6-2%	0.905	7-17 L/m^2
Vinorelbine	30	80-90%/20-10%	0.18	25-40 L/m^2
Bendamustine	100	94-96%/6-4%	1.5	25L
Chlorambucil	6	99%/1%	0.112	0.32L/kg
Pemetrexed	500	81%/29%	5.5	16.1L

Figure 1a. Doxorubicin free level with BSA dosing over BMI

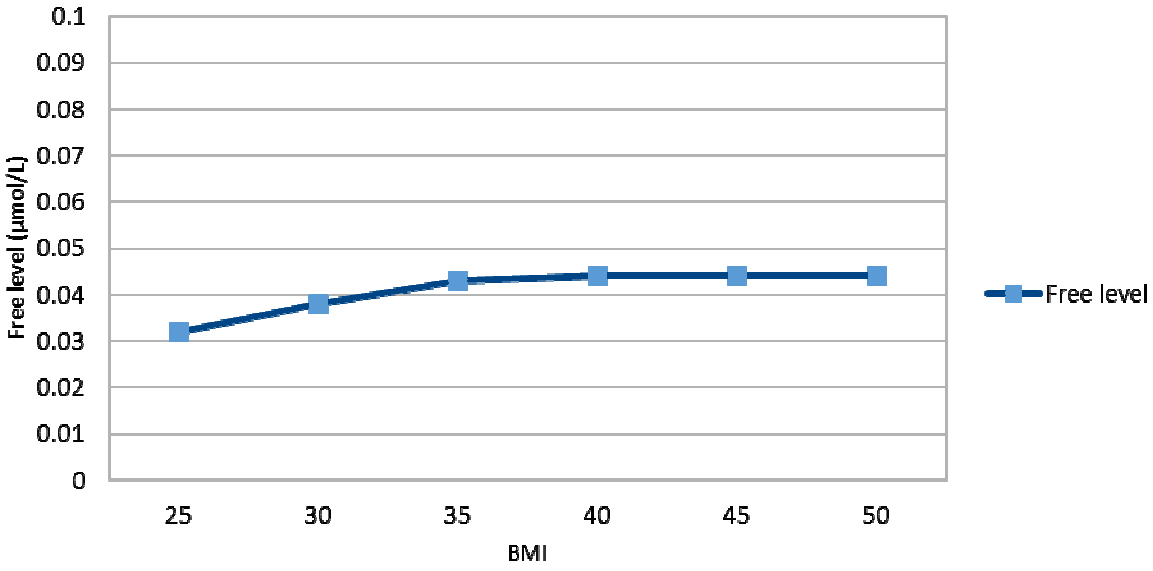


Figure 1b. Cisplatin free level with BSA dosing over BMI

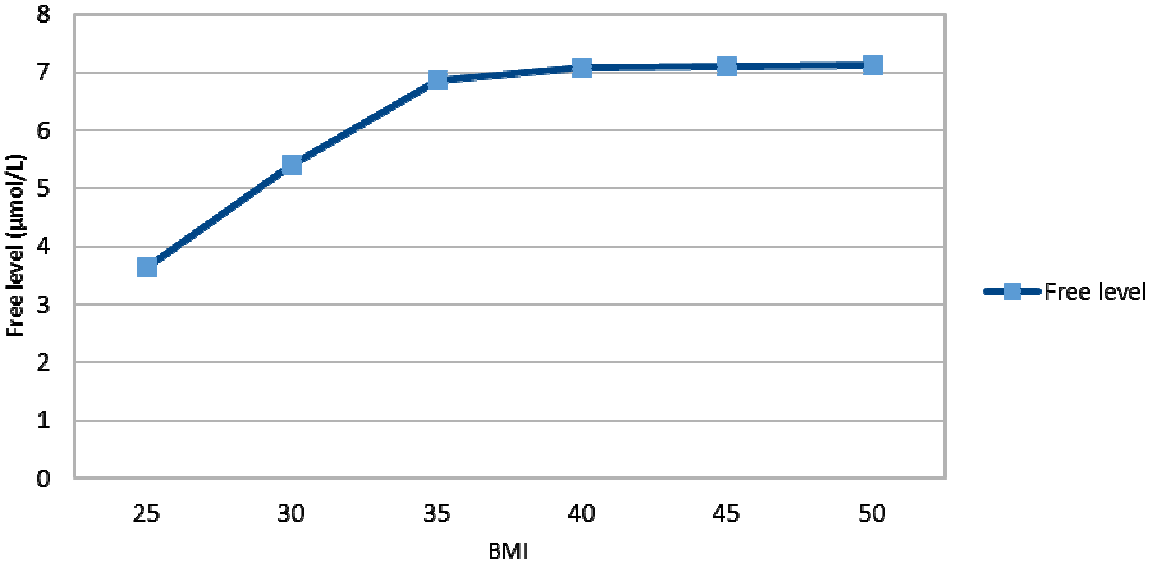


Figure 2a. Doxorubicin bound and free drug levels without dose reduction

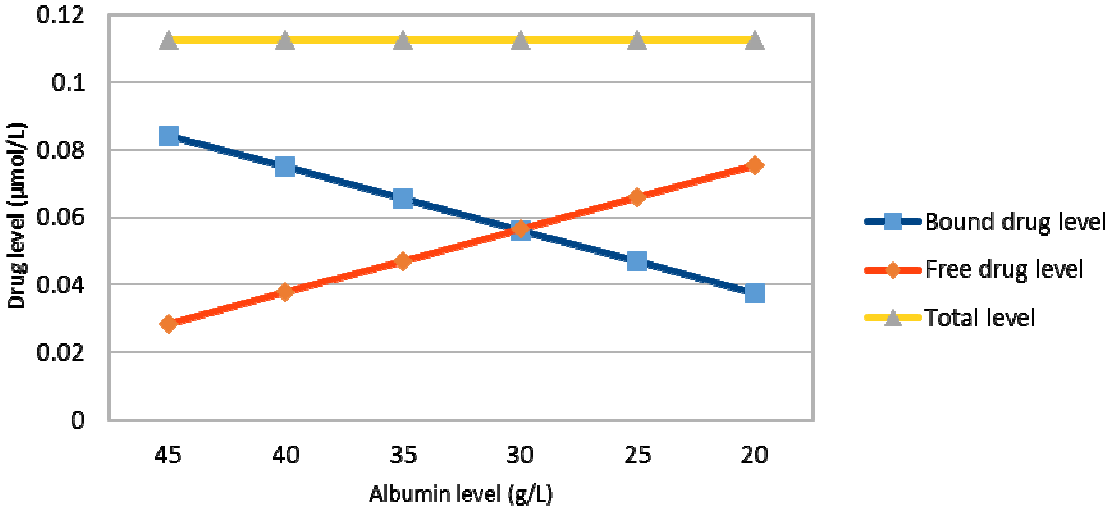


Figure 2b. Cisplatin bound and free drug levels without dose reduction

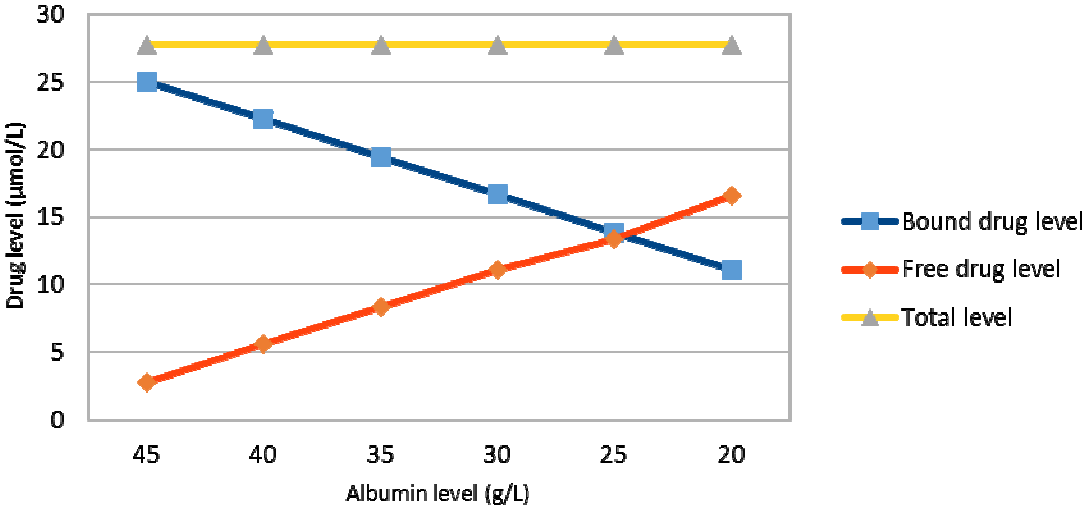


Figure 3a. Doxorubicin bound and free drug levels after dose reduction

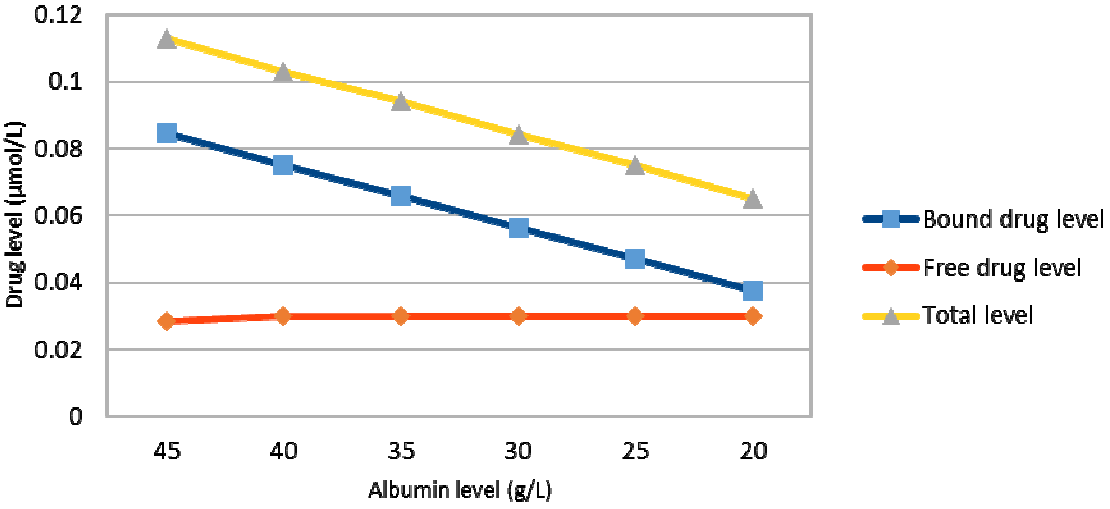


Figure 3b. Cisplatin bound and free drug levels after dose reduction

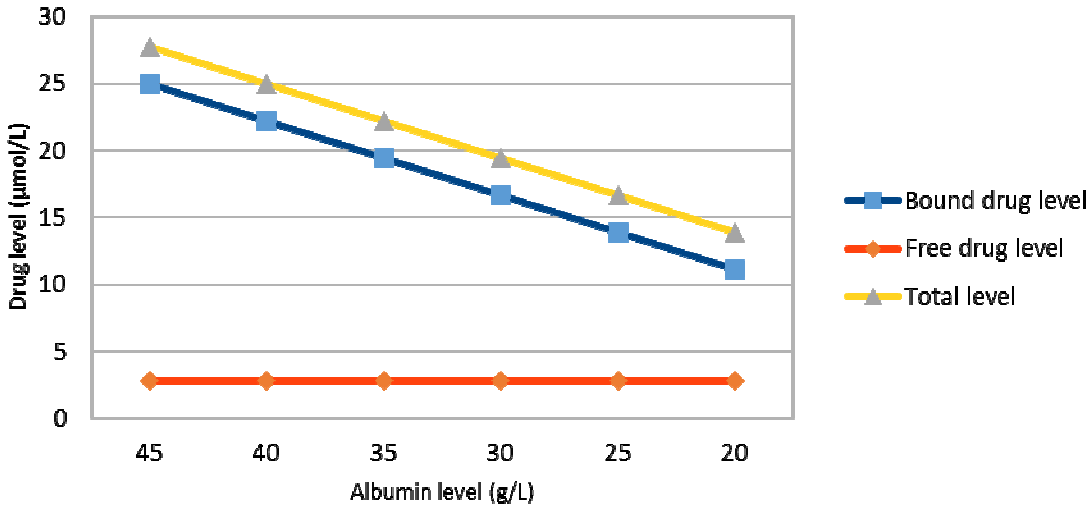
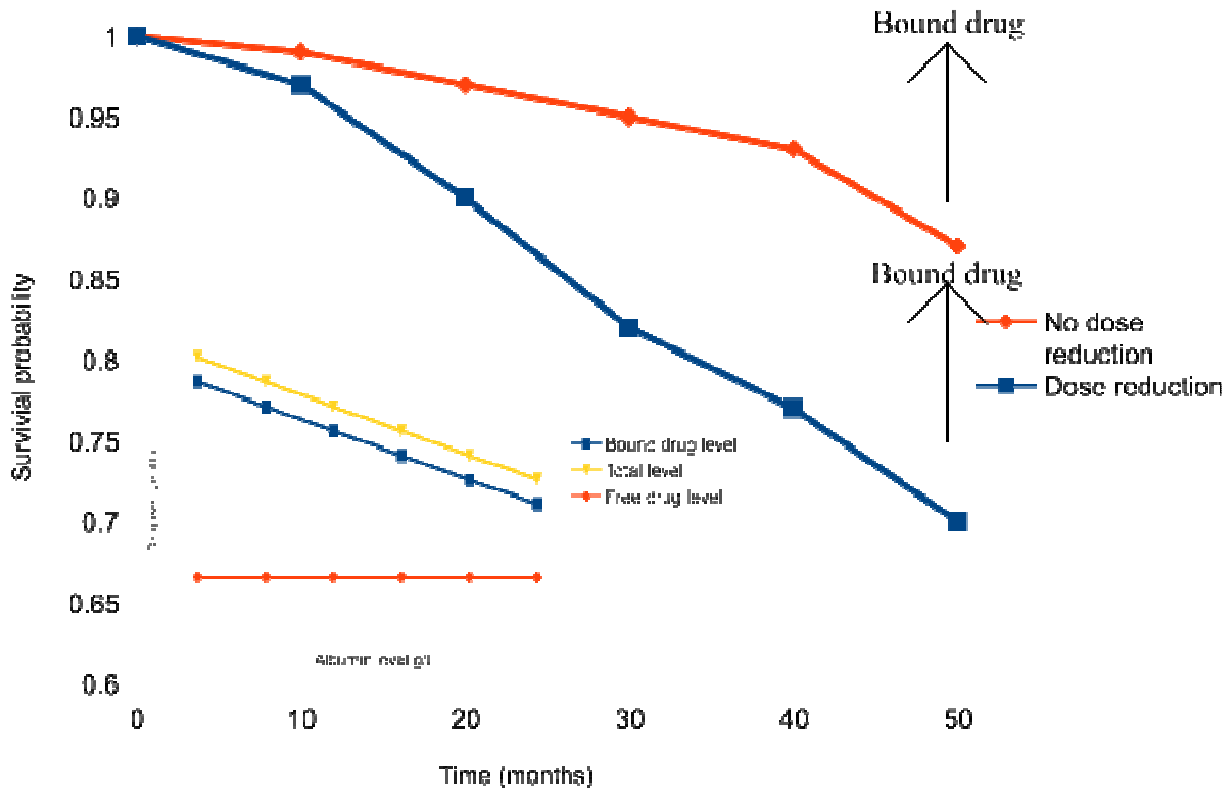


Figure 4. Superimposed dose-reduced chemotherapy over survival curve data.



APPENDIX

Lean Body Weight male =(9270 x total body weight)/\(6680 + (216 X BMI)

Ideal Body Weight male = 50kg + 2.3kg for each inch over 5 feet

Equations
Vd= drug dose/serum drug concentration
n(Pt)= [(1/fu-1)/K]
albumin binding capacity = n(Pt)/albumin g/L

Dose (µmol) = Drug dose/Molecular weight

Bound drug dose (µmol) = Percent protein binding (%) x Dose (µmol)

Free drug (µmol) = (Bound drug dose (µmol)) x Dose (µmol)

Albumin-drug binding capacity (µmol/g) = Bound drug dose (µmol)/ 337g albumin

n(Pt) = Albumin-drug binding capacity (µmol/g) x 45g/L(normal albumin level)

Binding affinity = (1/fu-1)/n(Pt)

Albumin reference range calculations.

If albumin was treated like a medication than Vd=Dose/Serum concentration
Vd(albumin)=337g(total albumin)/45g/L
Vd(albumin)=7.5L
Volume of distribution divided by BSA of 1.94 m^2 (height 180cm, weight75kg)
Volume of distribution per BSA = Vd(albumin)/BSA
Vd albumin/BSA m^2=7.5L/1.95m^2
Vd albumin/BSA m^2=3.87L/m^2

Albumin deficit correction calculation.

Total patient albumin= 4.5g/kg x (wt kg) (IBW or LBW) x patient's albumin serum level g/L)/45g/L

Total albumin based on weight = 4.5g/kg x (wt kg) (IBW or LBW)

Albumin deficit= Total albumin based on weight – Total patient albumin

Doxorubicin normal patient calculations (75kg and 337 grams albumin)

BSA 1.94 m^2 (180cm and 75kg)
Dose (mg) = 75mg/m^2 x 1.94m^2 = 145.5mg
Dose (µmol) = Dose (g)/MW (g/mol) = 145.5x10-3g/543.52g/mol = 266 µmol
Bound drug (ppb 75%) = 0.75 x 266 µmol = 199.5 µmol
Free total drug = 266 µmol - 199.5 µmol = 66.6 µmol
Albumin binding capacity (µmol/g) = 199.5 µmol/337g = **0.59 µmol/g**
Vd = 1.94 m^2 x 1214L/ m^2 = 2355.16 L
Free drug concentration = Free total drug/Vd = 66 µmol/2355.16 L = **0.0284 µmol/L**

Cisplatin normal patient calculations (75kg and 337grams albumin)

BSA 1.94 m^2 (180cm and 75kg)
Dose(mg)= 100mg/m^2 x 1.94m^2 = 194mg
Dose (µmol) = 194x10^{-3}g/300.01g/mol = 646 µmol
Bound drug dose (ppb 90%) = 0.90 x 646 µmol = 581.4 µmol
Free total drug (µmol) = 646 µmol - 581.4 µmol = 64.6 µmol
Albumin-drug binding capacity (µmol/g) = 581.4 µmol/337g albumin = **1.729 µmol/g**
Vd = 1.94 m^2 x 12L/ m^2 = 23.28L
Free drug concentration = Free total drug/Vd = 64.6 µmol/23.28L= **2.78 µmol/L**

Example Cisplatin free calculation for BMI 50

BMI 50kg/m^2 = 180cm height and 162kg weight
BSA=2.69 m^2
Cisplatin dose 100mg/m^2 x 2.69 m^2 = 269mg or 897 µmol
Patient is over BMI of 40 so LBW is used versus IBW
LBW= 85.9 kg
LBW 85.9kg x 4.5g/kg = 398grams albumin
Albumin-cisplatin binding 1.73µmol/g x 389 grams = 667 µmol Bound drug
Total drug 897 µmol⁻ 667 µmol Bound drug = 230 µmol Free drug
Free drug 230 µmol/ Vd 32.28L = 7.13 µmol/L free drug level

Example Cisplatin free and bound levels without dose reduction at 25g/L albumin

BSA 1.94 m^2 (180cm and 75kg) Vd 23.28L
Cisplatin dose 100mg/m^2 x 1.94 m^2 = 194mg or 646 µmol
Total albumin 75kg at 25g/L= 75kg x4.5g/kgx 25g/L/45g/L=187.5grams
Total bound drug = 1.73 µmol/g x 187.5 grams = 324 µmol
Free drug = Total dose 646 µmol – Bound drug 324 µmol = 322 µmol
Total drug level = 646 µmol/ 23.28L = 27.75 µmol/L
Bound drug level = 324 µmol/23.28L = 13.92 µmol/L
Free drug level = 322 µmol/ 23.28L = 13.83 µmol/L
Fraction unbound = 13.83 µmol/L/27.75 µmol/L = 0.49 **or 49%**

Example Cisplatin free and bound levels with dose reduction at 25g/L albumin

Free drug level capped at 2.79 µmol/L
Free drug total = 2.79 µmol/L x 23.28L = 64.71µmol
Bound drug from above 259 µmol
Total dose = free drug 64.71µmol + bound drug 324 µmol = 389.42 µmol or 116mg
Total drug level 389.42µmol/23.28L = 16.73 µmol/L
Bound drug level 13.92 µmol/L
Free drug level 2.79 µmol/L