Leveraging protein binding and the EPR effect in legacy chemotherapy regimens.

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Editorial

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Notwithstanding standard or dose-dense protocols, response rates, Gompertzian growth curves and the Norton-Simon hypothesis; it is impossible to predict the outcome of chemotherapy for any particular individual. These sobering words demonstrate that much progress remains to be made in understanding and optimizing chemotherapy regimens.

Gupta and Lis (1) performed a systematic search of the literature using the MEDLINE database (January 1995 through June 2010) to identify epidemiologic studies on the relationship between serum albumin and cancer survival. In the 26 out of the 29 studies reviewed of cancers of the gastrointestinal tract, 9 out of 10 studies of lung cancer, 6 studies of female cancers and 8 studies of other cancer sites, higher serum albumin levels were associated with longer survival in multivariate analysis. Per the authors, a critical gap for demonstrating causality, was the absence of clinical trials demonstrating that raising albumin levels by means of intravenous infusion or by hyperalimentation decreased the excess risk of mortality in cancer patients. Numerous studies have confirmed that preoperative serum albumin, either by itself or in combination with inflammatory biomarkers (such as the Glasgow prognostic score (GPS) and the albumin to globulin ratio (AGR)), is an independent prognostic predictor of survival in various cancer types; in some instances, increasing the median survival tenfold when compared at albumin levels of <25 g/l and >35 g/l (2).

Albumin turnover is increased in tumor cells because they metabolize plasma proteins such as albumin more efficiently than amino acids to cover their increased need for energy. Due to the leakiness of tumor vessels, the extravasation of preferentially metabolizable macromolecules such as albumin is further upregulated via the EPR effect. Therefore, albumin may be the quintessential tumoricidal drug carrier; abundantly available (constituting greater than half of the protein in human blood plasma),

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capable of binding hydrophobic drugs and possessing a selectivity for tumor cells. The reference range for human serum albumin (HSA) concentrations in the serum is 35-50 g/l. It has a blood half-life of ~ 20 days.

However, this selective targeting effect of antitumor drugs bound to albumin in situ only appears to manifest at equimolar concentrations. Higher molar loading ratios of drug to albumin lead to accumulation in the liver, rather than in the tumor. It is thought that the native structure of albumin is altered at increased molar ratios. Consequently, such modified albumins are rapidly eliminated by the reticulo-endothelial system of the liver. The first commercialized drug specifically molecularly designed to take advantage of non-covalent binding to circulating albumin; insulin detemir; can be administered at a dose of 3 ml per day (14.2 mg/ml). It is notable that, at this dose, the molar ratio of albumin to drug translates to ~ 300:1.

Tables 1 and 2 show that the effect of supplementing a chemotherapy course with albumin is to effectively decrease the drug to albumin ratio closer to 1.

In so doing, the hydrophobic binding of drugs to albumin may occur without substantial alteration of the native albumin quaternary structure. Consequently, the drug-albumin complex is more likely to be spared from elimination by the cells of the hepatic monocyte macrophages. The resultant circulating macromolecular-drug complex should preferentially extravasate into the tumor by the EPR effect thereby increasing the selectivity, and efficacy, of the chemo- therapeutic drugs.

This proposed, as yet unpublished, in the literature, mechanism by which albumin improves the selectivity of chemotherapeutic drugs is consistent with epidemiological and animal loading studies. It also appears to be non-coincidentally consistent with the total dose in a course of chemotherapy, such that albumin supplementation decreases the molar ratio of albumin to drugs to a number closer to 1; in line with its level being an independent prognosticator in predicting median survival. The proposed mechanism does not involve new chemical entities (NCE), covalent bonding or new formulations. Hence, there is no regulatory burden on commencing these modified protocols.

Table 1 The effect of albumin supplementation on albumin to total API mole ratio

CHOP[c]	DOSE (mg/m^2[b])	MOLES/60 kg BODY MASS[b]	DRUGS TO ALBUMIN MOLE RATIO[d]	
			Without albumin supplementation	With albumin supplementation[a]
Cyclophosphamide	750	4.60×10^{-3}	2.4	1.3
Doxorubicin	50	1.47×10^{-4}		
Vincristine	1.4	2.72×10^{-6}		
Prednisolone	40	1.76×10^{-4}		

a. At the maximum albumin adult recommended dose of 2 g/kg
b. Surface area of 1.6 m^2 for 60 kg adult.
c. Chemotherapy regimen used for non-Hodgkin lymphoma. Although this regimen has now been superseded by the addition of bio-therapeutics, the principle of the drugs to albumin mole ratio being the causative factor behind preoperative and/or pre-chemotherapeutic albumin as an independent prognosticator of survival is still applicable.
d. Albumin concentration in blood was assumed to be at the lower limit of the range at 35 g/l (reflective of hypoalbuminemia in cancer patients). All the albumin was assumed to be accessible and capable of binding with the infused drugs. The total blood volume was taken to be 4 l. The molar mass of albumin was taken as 67 Kda.

Table 2 The effect of albumin supplementation on albumin to total API mole ratio

ABVD[e]	DOSE (mg/m^2[b])	MOLES/60 Kg BODY MASS[b2]	DRUGS TO ALBUMIN MOLE RATIO[d]	
			Without albumin supplementation[a]	With albumin supplementation[a]
Doxorubicin	25	5.00×10^{-5}	1.61	0.87
Bleomycin	10	1.13×10^{-5}		
Vinblastine	6	1.18×10^{-5}		
Dacarbazine	375	3.29×10^{-3}		

a. At the maximum albumin adult recommended dose of 2 g/Kg
b. Surface area of 1.6 m^2 for 60 Kg adult.
d. Albumin concentration in blood was assumed to be at the lower limit of the range at 35 g/L (reflective of hypoalbuminemia in cancer patients). All the albumin was assumed to be accessible and capable of binding with the infused drugs. The total blood volume was taken to be 4 L. The molar mass of albumin was taken as 67 Kda.
e. Chemotherapy regimen used for Hodgkin lymphoma. Although this regimen has now been superseded by the addition of bio-therapeutics, the principle of the drugs to albumin mole ratio being the causative factor behind preoperative and/or pre-chemotherapeutic albumin as an independent prognosticator of survival is still applicable.

Since albumin can be administered immediately before the regimen, no admixture stability studies need to be performed for the drugs of interest with albumin solutions. To minimize plasma volume expansion that can result from administering additional albumin solution, it may even be possible to reconstitute lyophilized cakes with albumin solutions. In this case, however, stability admixture studies will need to be performed. Such a procedure will have the added advantage of partly complexing the drug even before infusion into the circulation. If the effect of such albumin supplementation chemotherapy regimens is statistically significant in prolonging survival, albumin solutions will perform a pivotal function other than their use as crystalloid plasma expanders. Albumin may act as an 'enabling excipient' in antineoplastic drug formulations, much as 'adjuvants' do in vaccine formulations. The simple mathematical calculations presented above can be used in conjunction with clinical data to determine the exact amount of albumin supplementation required for a particular chemotherapy regimen for an individual patient.

It is important to realize that the binding of existing hydrophobic drug formulation cocktails to an easily accessible pool of circulating albumin affords a significantly lesser cost to benefit ratio because it does not involve additional regulatory burden, has a testable proposed mechanism of action (as reported in this editorial) that is consistent with epidemeological and clinical data and can be patient individualized for maximum efficacy. The proposed mechanism of action explains why existing epidemeological data report increased survival times using albumin supplementation. While there is no denying that significant amount of research dollars have had albumin microspheres, liposomes, dendrimers or PEGylated APIs gingerly eke out API specific efficacy niches, a near universal method that cost-effectively and simultaneously increases the efficacy of multiple molecules on already existing regimen platforms and leverages existing circulating or easily available supplementary albumin as a delivery system is more likely to succeed in prolonging survival times.

Legacy chemotherapy regimens have the potential to be significantly more effective and less toxic if the dosage is titrated so that the mole ratio of drugs to circulating albumin is ≤ 1 and the order of administration of the drugs

within each course of the regimen follows the sequence most hydrophobic (usually the least dose) to least hydrophobic (usually the largest dose).

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