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Impact of Hypoalbuminemia on Response and Toxicity of Antineoplastic Agents in Patients Diagnosed With Solid Malignancies

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ABSTRACT

Low serum albumin level is common in patient with cancer with reported incidence of 40 %– 50%. Hypoalbuminemia is associated with altered protein binding of antineoplastic agents, which in turn affect the pharmacological action of the drug. The objective of this review paper was to find original research paper that reports the association of hypoalbuminemia and outcome of highly protein bound antineoplastic agents. All relevant articles that described the objective were included in the review. We found that, Hypoalbuminemia was related to discontinuation of treatment due to toxicity. Study on toxicity of cisplatin and paclitaxel in Non-Small Cell Lung Cancer was associated with decreased serum albumin level. Decrease in protein binding was observed in presence of hypoalbuminemia. For example, Clearance time of methotrexate was high in patient with hypoalbuminemia.

I. INTRODUCTION

Solid tumours contain abnormal and heterotypic cells that communicate through tight and gap junctions. In contrast with liquid tumours, as the cells multiply, they form a "mass" called a solid tumour and usually do not contain pockets of fluid, pus, air, or other substances. Solid tumours can be either non-cancerous (benign), pre-malignant (cells that have the potential to become malignant), or malignant (cancerous). Solid tumours represent approximatively 90% of adult human cancers. They can develop in many parts of the human body, including the breast, lung, prostate, colon, melanoma, bladder, and kidney. The estimated number of incident cases of cancer in India for the year 2022 was found to be 14,61,427 (crude rate:100.4 per 100,000). In India, one in nine people are likely to develop cancer in his/her lifetime. Lung and breast cancers were the leading sites of cancer in males and females, respectively. The incidence of cancer cases is estimated to increase by 12.8 per cent in 2025 as compared to 2020. [1] [2]

The Human Serum Albumin, having a molecular weight of 66.5 kDa, is the most abundant plasma protein with a large drug binding capacity. Most of the anti- cancer drugs have high affinities for binding sites on the albumin molecule. Pharmacologically, albumin binding has 3 implications 1. Only unbound drug can exert pharmacological actions. 2. Only unbound drug is able to distribute into body tissues 3. Only unbound fraction of drug is available for elimination from vascular compartments.[4] Therefore, serum albumin level will have a prominent effect on the pharmacokinetic properties of albumin- bound drugs.

As per the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, hypoalbuminemia is defined as "a disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.[3] Among cancer patients, the prevalence of hypoalbuminemia is common.Most of antineoplastic agents have higher affinity to binding sites of albumin. Decreased serum albumin level leads to a larger amount of unbound drug molecules in the serum which are distributed into tissue in a larger extent when compared to 'normal'

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albumin binding. This may lead to increased response or even toxicity of highly protein bound drugs.

In this work, we review the English literature on association of hypoalbuminemia on response or toxicity of antineoplastic agents. We also provide the body of evidence on impact of hypoalbuminemia on outcome of highly protein bound antineoplastic agents.

SEARCH STRATEGY AND SELECTION CRITERIA

Data for this review were obtained from systemic searches on PubMed as well as reference cited by relevant articles. Search terms included hypoalbuminemia, solid malignancies, albumin binding, or highly protein bound antineoplastic agents.14Articles were obtained through these systematic searches. Only English language papers that described the association of hypoalbuminemia on outcome of oncolytic therapy were reviewed.

II. DATA ANALYSIS

POTEIN BINDING OF ANTINEOPLASTIC AGENTS

Plasma protein binding is a critical parameter of drugs because a free drug is thought to elicit a pharmacological effect and be cleared from the body. A variety of compounds tend to bind slightly more to human plasma compared to pre-clinical species. The disposition of a drug can be affected by the formation of drug-plasma protein adducts. Human plasma proteins that bind to small-molecule drugs.[22]

Tyrosine Kinase Inhibitors (TKI) are a group of pharmacologic agents that disrupt the signal transduction pathways of protein kinases by several modes of inhibition. Acrylamide of covalent TKIs can covalently bind to lysine residue of HAS. The covalent binding is of species difference, especially between animal and human. The result of molecule docking explained the binding mode of covalent TKIs and HSA.[23]

Table 1: Protein binding of antineoplastic agents

Anticancer agents	Protein binding (%)	Reference
Afatinib	93	[24]
Axitinib	98	[25]
Imatinib	98	[26]
Lenvatinib	90-92	[27]
Pazopanib	>99	[28]
Regorafenib	>99	[29]
Sorafenib	>99	[30]
Sunitinib	94	[31]
Vemurafenib	NA	[32]

CAUSES OF HYPOALBUMINEMIA

Hypoalbuminemia is defined by albumin serum levels lower than 35 g/L. However, it usually becomes clinically significant for levels < 25 g/L (Gatta et al., 2012). Cancer patients undergo high physiological stress as a result of tumour necrosis and tissue damage.[15] The body attempts to naturally counteract these changes by releasing proinflammatory cytokines and growth factors, which may in turn decrease production of albumin. [13]Likewise, increased vascular permeability may lead to decreased serum albumin levels. [14].In addition, cancer patients commonly experience a nutritional and functional decline; reduced food intake can have a small impact on albumin levels [15].

The incidence of hypoalbuminemia varies by cancer type, severity of disease, and patient status, one observational cohort study reported that 164 of 200 (82%) critically ill cancer patients had at least grade 1 hypoalbuminemia, with a mean albumin concentration of 1.82 g/dL. Considering a demonstrated incidence of hypoalbuminemia in the critically ill population (not limited to the oncology setting) of 40% to 50%, hypoalbuminemia in the cancer population appears to be more common.

IMPACT OF HYPOALBUMINEMIA ON RESPONSE AND TOXICITY OF ANTINEOPLASTIC AGENTS

Altered concentrations of serum proteins often accompany malignant disease. In case of hypoalbuminemia a larger amount of unbound drug is able to distribute into body tissue. These unbound drugs are able to exert pharmacological action, that may lead to toxicity.A study was

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conducted by Joshua L. Murdock Demonstrated tolerability of highly protein bound oral oncolytic agents in patient with hypoalbuminemia. Thisincludes 143 patients receiving oral oncolytic agents. Therapy discontinuation rate was higher in patient with hypoalbuminemia.[18] Patients with hypoalbuminemia are at increased risk for toxicity due to short duration of therapy discontinuation.

Another study conducted by Jessica Marini aimed to evaluate the relationship between hypoalbuminemia and Adverse Drug Reaction of antineoplastic agents. This retrospective study included 101 patients with hypoalbuminemia receiving Tyrosinekinase inhibitors(TKI). The patient with baseline hypoalbuminemia had high rate of TKI discontinuation when compared to patient with normal albumin level. Incidence of hypoalbuminemia in this study was 46%.[21]

Majority of the study that is reviewed concluded with discontinuation of treatment due to toxicity in patient with hypoalbuminemia when compared with patient without hypoalbuminemia. Maintaining dose intensity is important for patient receiving oncolytic therapy and hence albumin must be monitored throughout the treatment cycle. Supportive care should be given to patient with hypoalbuminemia..[18].[21].

Ref.	Design	Objective	Sample size	Findings	Comments
[17]	Retrospective study	To describe the impact of hypoalbuminemia on oral oncolytic drug tolerability	143	Patient with hypoalbuminemia is at increased risk of treatment discontinuation due to toxicity	Toxicity was not documented due to short duration of discontinuation of treatment
[21]	Retrospective study	To evaluate the relationship between hypoalbuminemia and TKI tolerability in patients with solid-tumor malignancies.	220	Hypoalbuminemia was associated with earlier and higher incidence of tyrosine kinase Inhibitors discontinuation when compared to patient without hypoalbuminemia in solid malignancies	Severity of Adverse events was not assessed due to retrospective study design
[20]	Retrospective cohort study	to assess serum albumin's relationship with methotrexate pharmacokinetics	167	hypoalbuminemia was associated with increased time to MTX clearance and increase length of hospitalization	A powered study that matches the baseline characteristics is necessary to confirm the observation
[19]	Prospective study	to associate malnutrition and albumin serum levels with the occurrence of chemotherapy-induced toxicity in cisplatin plus paclitaxel chemotherapy-treated NSCLC.	100	Chemotherapy-induced toxicity in NSCLC patients treated with paclitaxel and cisplatin was associated with malnutrition and hypoalbuminemia	Study is evident enough to show the association of hypoalbuminemia and toxicity of cisplatin and paclitaxel

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III. DISCUSSION

The review is aimed to present association of hypoalbuminemia and response or toxicity of antineoplastic agents.One of the articles highlighted that patient with hypoalbuminemia had longer time to methotrexate clearance in patient with leukaemia and lymphoma. Delayed Elimination of methotrexate caused due to increase in clearance time might have contributed to drug related toxicity in patients. Several characteristics were identified to be different in patient with hypoalbuminemia that may contribute to delayed clearance which include concomitant use of nephrotoxic agents and fluid retention..[20]

A study conducted by Almasaudi AS et.al shows that hypoalbuminemia was associated with nutritional risk and Systemic Inflammatory Response. Therefore, Hypoalbuminemia reflects both nutritional and inflammatory status. [19]

Two articles were reviewed to understand the impact of hypoalbuminemia on outcome of tyrosine kinase inhibitors. Currently only minimal data is available regarding the link between hypoalbuminemia and TKI tolerability in patient. The analysis shows higher incidence of liver dysfunction in patient with hypoalbuminemia. Tyrosine Kinase inhibitors are highly protein bound and thus hypoalbuminemia was the leading cause for early discontinuation of Tyrosine kinase inhibitors therapy because of toxicity.[18].[21]. However, due to the nature of study and decreased sample size toxicity grading was not done in both the study. Thus, further studies are warranted to identify the relationship between hypoalbuminemia and clinical outcome of highly protein bound antineoplastic agents.

IV. CONCLUSION

The prevalence of hypoalbuminemia is common among patients with cancer. Most of the anticancer drug have affinity to the binding site of albumin, which is the most abundant plasma protein. Thus, decrease in serum albumin level will contribute to altered response or even toxicity of highly protein bound drug. Till dateonly limited data is available to demonstrate the incidence of toxicity of highly protein bound antineoplastic agents in patient with hypoalbuminemia. Majority of study was of retrospective design and data collected were from providers' information on toxicity and discontinuation of treatment. Hence a powered study with large sample size is required to back up the observations of these study. The effects of hypoalbuminemia on response of antineoplastic agent are more controversial due to the lack of data on this topic.

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