

# Renal Adverse Effect in Solid Cancer Patients Treated With Cytotoxic Agents

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**Abstract** – Severe or pertinent nephrotoxicity interferes with cytotoxic chemotherapy resulting in dose reductions, treatment delays or cessation of therapy. Chemotherapy induced nephrotoxicity is associated with anaphylactic reactions, vascular complications, decreased renal perfusion and is relative to the cumulative dose intensity. Risk of nephrotoxicity is higher in the elderly and diabetic patients. Patients with previous nephro diseases such as nephritis and comorbidities i.e. anemia, malnutrition and renal damages are prone to an added risk of nephrotoxicity. This review consolidates the pattern of nephro adverse effects associated with each component of the cytotoxic agents regimen e.g. cisplatin, ifosfamide, carboplatin etc. Higher propensities of nephro adverse effects are associated with the cytotoxic agents, intensified by the incorporation of more than one drug at a time. In conclusion the nephro biomarkers like urinary kidney injury molecule- 1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), blood urea nitrogen, serum creatinine etc should be monitored in the patient under a cytotoxic treatment plan as well as purposefully assessed during follow-up visits of the patients.

**Keywords** – Renal, Cytotoxic, Cancer, Chemotherapy

## 1. Introduction

### General Side Effects of Chemotherapeutic Agents

Among the general adverse effect of chemotherapy nausea and vomiting are of great importance which is of stressful from the patient perspective. Chemotherapy nausea and vomiting (CINV) remains fully uncontrollable for a considerable number of patients receiving chemotherapy. Delayed nausea vomiting may occur after 24 hrs of treatment associated with increase dose of chemotherapeutic agents and with repeat cycle of therapy [1] Diarrhea is also the general side effect of chemotherapy, associated with treatment that consist of bolus fluorouracil (5-FU) and irinotecan. The prevalence of diarrhea in patients receiving chemotherapy has been estimated to be as high as 82%. Chemotherapy-induced diarrhea can lead to fluid and electrolyte losses, which will linked to life-threatening dehydration, electrolyte imbalances and renal insufficiency. Diarrhea is as complicating as chemotherapy induced neutropenia, leading to increased risk of infectious complications [2]. Sensory and motor nerve damage relating to Chemotherapy-induced peripheral neuropathy (CIPN) is one of the serious medical issues for many patients receiving anti-cancer therapy. Well documented chemotherapeutic agents causing CIPN, including platinum analogues, Vinca alkaloids, and taxanes produce dose limiting side effects. Sign and symptoms of CIPN are ataxia, myalgia, pain in extremities, muscles weakness and have signs of paresthesia. Peripheral

neuropathy is more frequently reported in patients treated with a regimen comprising of more than one cytotoxic agent [3]. Paclitaxel possess distinguished side effects of peripheral neuropathy [6]. Cognitive risks are also considerable side effects of many chemotherapeutic agents and patient aged 65 and above are at great risk. Chemo agents e.g. methotrexate, 5- Fluorouracil (5-FU), and taxanes that possess toxic effects on peripheral nervous system [4] and agents that have documented CNS toxicities(e.g., cyclophosphamide, methotrexate, fluorouracil, and paclitaxel)are need to examine for cognitive risks in patients receiving chemotherapy [5]. Ovarian function is affected by chemotherapy. Females of child bearing age receiving chemotherapy sensitive toward reproduction and chemotherapy are prone to infertility, premature menopause. Follicular atresia and follicular pool destruction are associated factors. Reproductive defects are unpredictable and can lead to long-term health problems such as cardiovascular diseases and osteoporosis. Alkylating agents such as cyclophosphamide and ifosfamide are particularly toxic to the oocyte. In men Chemotherapy can impede reproductive ability and libido and is quite more injurious to male fertility than to female fertility [7]. Consequently, all alkylating agents i.e. ,ifosfamide, cyclophosphamide and procarbazine are gonadotoxic [8].The most frequently occurring toxicities of chemotherapeutic agents are gastrointestinal disturbances, bone marrow suppression, and alopecia which are an outcome of direct toxicity of chemo

agents to the rapidly dividing cells of the bone marrow, gastrointestinal tract, and hair follicle, respectively [9].

### **Hematological and Non Hematological Adverse Effect**

There are two types of adverse effect hematological and non-hematological; former will interfere with blood cells which primarily take place in bone marrow [10]. The mature blood cell has been continuously replaced according to basal need and requirement of our body [11].

Hematological disorders are at high potential risk as compare to non-hematological disorder [12]. Some agents cause predictable hematologic disease e.g antineoplastic and other induces idiosyncratic reaction not linked with drug. Drug induced hematologic disorder may include thrombocytopenia [10-12], Neutropenia is decrease in circulating neutrophil which is caused by major cytotoxic drug used in breast cancer known as Docetaxal [13,14], agranulocytosis is caused by clozapine to avoid this complication it is preferred to add filgrastim [15], different types of anemia are seen with chemotherapeutic agents which have great impact on quality of life of these patients e.g megaloblastic anemia, aplastic anemia and hemolytic anemia [10-12].

Hematopoietic system consist of three primary cell 1) leukocyte 2) platelets 3) erythrocytes where as non-hematological drug induced adverse effect cover other parts of the body(10) e.g. cardiac toxicity is caused by renal treatment drugs Sunitinib and sorafenib [16], hepatic toxicity which is caused very rarely more cases are reported idiosyncratic drug reactions [17], dermatology toxicity is the most commonly seen toxicity by all drugs in which cutaneous eruption is mostly seen [18], neurological and nephrology toxicities is frequently seen in ovarian cancer patients. Cisplatin is most effective drug used to treat this disorder and causes these toxicities too; other toxicities are Genital problem and respiratory issues [19].

### **Types of Renal Toxicities**

Nephrotoxicity remains a troublesome complication of chemotherapeutic agents. A number of kidney lesions can result from these drugs, together with primarily tubular-limited dysfunction, full-blown acute kidney injury, glomerular injury with proteinuria and long-term chronic kidney injury [20]. Vascular complications coupled with antineoplastic agents are being reported with increasing incidence. Such vascular toxicity is clinically diverse ranging from asymptomatic arterial lesions to a fatal thrombotic microangiopathic syndrome. The conclusion from the studies suggest that there may be two types of mitomycin-related renal problems that it is due to a direct toxic effect of mitomycin to the renal arterial endothelium system and leads to fibrin thrombi deposition in the microvasculature of the kidney [21]. An antineoplastic drug i.e. Cisplatin remains a most important drug for the management of solid tumors. It causes a major dose-limiting side effect i.e. nephrotoxicity, which progresses gradually and predictably after initial and repetitive exposure. The kidneys accumulate cisplatin to a higher quantity than other organs possibly via mediated transport. Functionally, decreased renal perfusion and a concentrating defect exemplify its nephrotoxicity [22]. The mechanisms, through which cisplatin produces its nephrotoxicity are intricate and involve inflammation, oxidative stress, apoptosis and fibrogenesis. These measures

cause problems like tubular dysfunction and tubular damage with sodium, potassium, and magnesium wasting. Some patients have an irreversible decrease in glomerular filtration but the majority patients have a reversible reduction in glomerular filtration [23]. A most severe complication among the ifosfamide intoxications are neurotoxicity and nephrotoxicity [24]. The progression of renal Fanconi syndrome is associated with a cytotoxic treatment of ifosfamide. Whereas, the structural isomer of ifosfamide that is cyclophosphamide is associated with growth defects in children and bone defects in adults [25]. Adverse effects cause by Imatinib in patients is of significant number who displays either unusual or delayed adverse effects. The adverse events can involve cardiac, renal, dermatologic problems and fluid retention [26] Patients using imatinib for the treatment of chronic myeloid leukemia (CML) can have problems like acute kidney injury and chronic renal failures, in those patients' investigations are carried to find out that there is a relation between duration of imatinib therapy and reduction in glomerular filtration rate (GFR) [27]. Tacrolimus (TAC) and Cyclosporine (CSA) have important adverse effects, particularly nephrotoxicity. Both Cyclosporine and Tacrolimus have renal hemodynamic effects which causes rapid reductions in glomerular filtration rate which are reversible upon dose reduction or cessation in early phase. Ultimately, glomerular filtration rate loss may become irreversible, reflecting structural changes, including glomerulosclerosis, interstitial fibrosis, arteriopathy and tubular atrophy [28].

### **Biomarkers of Renal Toxicity**

Most commonly used serum biomarkers are serum creatinine (SCr) and blood urea nitrogen (BUN), which help detect renal toxicity in usual clinical practise. A considerable alteration in glomerular filtration rate (GFR) and in other parameters of renal function is apparent only after significant injury has occurred. BUN is extensively used but not a good parameter for measure of renal injury as it is affected by many other factors. Glomerulus filtered BUN freely, but many parts of nephron reabsorbing of urea, as a result, in volume depletion without existence of tubular injury an increase in BUN can also be seen. Several other biomarkers are there which help predict human nephrotoxicity and the site of renal injury, which are inclusive of neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), urinary kidney injury molecule- 1 (KIM-1), cystatin C, clusterin, fatty acid binding protein liver type (L-FABP) and osteopontin. [29]. Enzymes released from injured tubular cells are useful in detecting many clinical conditions including acute and chronic renal injury [30]. Cytoplasmic, lysosomal or membranous protein gives info about nature and degree of injury. Such as cytoplasmic enzymes  $\alpha$ -glutathione S-transferase specific for proximal and p-glutathione S-transferase (GST) isomers are specific for distal tubular epithelial cells [31] and increased excretion of these proteins in urine provides information of cellular injury. Methotrexate toxicity is indicated by augmented discharge of lysosomal enzyme N-acetyl-glucosaminidase (NAG), found in proximal tubules [32, 33]. Indicate injury to tubular cells and increased concentration of this enzyme also proposes increased lysosomal activity without cell disruption [34]. Mostly enzymes in tubular urine are alkaline phosphatase (AP), c-

glutamyl transpeptidase (cGT) and ala-(leu-gly)-aminopeptidase belongs to brush border [35] and enhanced excretion of these enzymes indicate brush border membrane injury with loss of microvillous structure and considerable loss of these structure result in reduced reabsorption and amplified excretion of filtered proteins such as b<sub>2</sub>-microglobulin and retinol-binding protein [34] TNF- $\alpha$  have important role in cisplatin nephrotoxicity. In invitro studies ,it is observed that cisplatin stimulates renal epithelial cells to produce TNF- $\alpha$  lead to the possibility that renal parenchymal cells are the major source of TNF- $\alpha$  in cisplatin nephrotoxicity [36] Biomarkers of acute kidney are matrix metalloproteinase-9 (MMP-9), kidney injury molecule-1 (KIM-1), and N-acetyl-b-Dglucosaminidase (NAG) which are excreted in urine [37]. Biomarkers discussed above can be categorized into the following three types: 1) enzymes: e.g., alanine aminopeptidase (AA), -glutamyl transpeptidase (-GT), NAG, alkaline phosphatase (AP), lysozyme, and lactate dehydrogenase (LDH), cathepsin B, microglobulin and retinol-binding protein (proteins) and GST, clusterin, CYR-61, NGAL, and F-actin which are kidney derived antigens. These biomarkers are assessed and developed in varying models of nephrotoxicity [38].

#### **Management and Treatment Protocol of Drugs Causing Renal Toxicities**

The side-effects linked with targeted therapy should be managed by practicing physician/oncologist by using supportive and pharmacologic interventions. Severe toxicity and side effects may involve external specialist consultation and treatment suspension and/or dose reduction [39]. For the prevention of acute kidney insufficiency sufficient volume repletion is of major importance, however renal failure will not always corrected by fluid deficit. Hyperoncotic solutions are not optional because of their renal risk but fluid resuscitation with crystalloids is safe and effective. No method has verified to be advanced, but careful management is essential for improving outcome like renal replacement therapy is a life-sustaining intervention that can provide a bridge to renal recovery [40]. Nephrotoxicity induced by cisplatin can be reduced drastically by vigorous hydration with saline and simultaneous administration of mannitol before, during, and after cisplatin administration. An agent Procainamide without varying the antitumor activity of cisplatin protects against the nephrotoxicity produce by it. The combination of ebselen and allopurinol also reduces cisplatin causing nephrotoxicity and ototoxicity. Amifostine, an organic thiophosphate donate a protective thiol group which decrease cisplatin-induced toxicity i.e. nephrotoxicity [41]. Pretreatment with pravastatin distinctly reduces carboplatin causing renal tissue injury and ameliorated renal dysfunction [42]. Sunitinib, a member of the rapidly expanding family of vascular endothelial growth factor receptor (VEGFR) and multitargeted tyrosine kinase inhibitors (TKIs), is initial therapy for metastatic clear cell type renal cell carcinoma [43]. Ifosfamide induce nephrotoxicity which is due to its selective uptake by human organic cation transporter 2 (hOCT2) into renal proximal tubular cells. This toxicity can be prevented by the co administration of cimetidine [44]. Amifostine may provide renal protection during peptide receptor radionuclide therapy

using somatostatin analogs, both by alleviation of radiation damage and the presently observed decrease of absorbed kidney radiation dose [45]. Calciphylaxis is a rare, yet life-threatening disease mostly occurring in dialysis patients. A multi-modal treatment of calciphylaxis with persistent hyperparathyroidism, using IV sodium thiosulfate, sevelamer and cinacalcet seems to progress the outcome of this devastating disease [46]. Eculizumab a monoclonal humanized antibody use as an intial therapy in patients with Kidney failure involves dialysis, adjacent to the complement component C5. After one week from the first administration, there is a significant improvement of all clinical and laboratory parameters with complete recovery from hemodialysis, even in the presence of systemic infections. This reveals that complements inhibiting treatment with the drug permit the protection of renal function and evade disease relapses during systemic infections [47]. Procaine administration with cisplatin treatment mildly influences necrotic changes of renal proximal tubules and in concentration of BUN and creatinine because of cisplatin administration. Kidney platinum level and level of TNF- $\alpha$  mRNA is not affected by the administration of procaine with cisplatin but the p21 and HO-1 gene expression was not further promoted, rather markedly decreased in patients receiving cisplatin with procaine [48]. In mice lethal dose toxicity of cis dichloro diammine platinum (II) (DDP) (20 mg/kg), is prevented by Sodium thiosulfate. And it reduces the toxicity of DDP in a dose-related manner. Loss of weight induced by DDP is also reduced by concurrent administration of Sodium thiosulfate with DDP but it partially decreased the antitumor activity of DDP. Sodium thiosulfate (800 mg/kg) injected within 1 hour before or 1/2 hour after DDP blocked nephrotoxicity [49]. In order to prevent the effectiveness of cisplatin anti-tumor activity, WR-2721 Injection of 200 mg/kg was given 30 minutes prior to graded doses of DDP (cisplatin) which caused hindrance to produce nephrotoxicity induced by cisplatin. As an outcome, it was likely to administer doses of cisplatin which could be toxic without WR-2721 injection. WR-2721 can, prevent from the toxic side effects of cisplatin while side by side increases the efficacy of cisplatin therapy [50]. Moreover, the standard treatment including cyclophosphamide and cisplatin , the administration of reduced glutathione in combination, produce resistance against cisplatin induced nephrotoxicity. Furthermore the pretreatment by glutathione will not affect therapeutic efficacy [51]. The toxic effect of cisplatin in young and adult rats was decreased by vitamin E, given 12 hr before cisplatin, but this effect could be enhanced by concurrent administration of vitamin E with vitamin C given 12 hr prior to cisplatin noted in 10- and 55-day-old rats devoid of any effect on the concentration of renal tissue platinum [52]. The selenium prevent with cisplatin-induced cataract formation and nephropathy in cancer patient when it is administered with high dose of vitamin E injection [53]. In the beginning stage of ifosfamide therapy, it causes renal toxicity. The administration of NAC decreases the severity and facilitate prevention of high levels of serum creatinine,  $\beta_2$ -microglobulin etc [54]. Mesna is a thiol compound, which has no antineoplastic activity, but it is used in combination with oxazophosphorine alkylating agents as an uroprotective agent. Mesna is considering in reducing the frequency of

bladder cancer & cystitis by working against the toxic effects of acrolein [55]. The administration of mesna with cyclophosphamide for the avoidance of bladder toxicity is a carry out resulting primarily from investigations with ifosfamide. Mesna must be used only in concurrence with the administration of high-dose cyclophosphamide, characteristically explained as 50 mg/kg or 2 gm/m<sup>2</sup> [56, 57].

### Quality of Life

Quality of life of cancer patient is always a question due to treatment adverse effects and toxicity caused by chemotherapeutics agents. Renal toxicity caused by these agents alter quality of life these patients. Renal toxicity can lead to functional impairment of the organ [58]. Cisplatin is the most effective drug used in treatment of ovarian cancer to minimize the neuro and nephro toxic effect it dose is tapered. Glutathione, tripeptide (glutamyl-cysteinyl-glycine, is used to reduces the adverse effect of cisplatin [19]. In end stage renal toxicity, anemia is major concern which affects the quality of life due to progressive symptoms associated with it. (E.g. fatigue, dyspnea) [59, 60]. Chemotherapeutics agent leads to hematological toxicities e.g anemia which has bad impact on quality of life of the patient. It is beneficial to maintain the haemtocrit normal level to improve the quality of life. The major problem forefront to normalized the haemtocrit level is cost. Cost of treatment is increased due to addition of higher epoetin doses and iron requirements [58, 60].

### 2. Conclusion

Considerable risk of nephrotoxicity is related with the first line agents employed for the management plan of patients with active disease. Nephrotoxicity is associated with the elevation of serum creatinine (SCr) and blood urea nitrogen (BUN), which should be objectively assessed during the course of treatment. The abnormal rise in enzyme levels (3-5 × of normal values) may require cessation of therapy even in the absence of symptoms. The nephritic status should also be assessed in the patients during follow-ups.

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