Nephrologist and haematological malignancies

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Acute kidney injury (AKI) is common in patients with different types of malignancies, reasons could be direct consequences of malignancy, related to adverse effects of chemotherapy or some other complications. Among all; haematological malignancies are more common to give rise to this scenario, especially multiple myeloma (MM), leukaemias and lymphomas. The pathological mechanisms may vary from cast nephropathy in MM, allogeneic haematopoetic stem cell transplantation (HSCT)[1] or leukostasis in cases of leukaemia, with chemotherapy like cisplatin related nephrotoxicity or obstructive nephropathy with rapid break down of cells, the tumour lysis syndrome. Newer therapies like immunotherapy with chimeric antigen receptor T (CAR-T), has been approved by FDA in 2017 for relapsed or refractory acute lymphoblastic leukaemia. Cytokine release syndrome has been reported in >40% of patients receiving CAR-T therapy[2] and this can also give rise to AKI.

A good understanding about the potential causes and mechanisms of kidney injury and timely addressing the problem and managing the patients is the responsibility of a nephrologist.

Multiple Myeloma

There occurs abnormal proliferation of clones from B cell lineage, including plasma cells, thus also named as monoclonal gammopathy. Free light chains of involved immunoglobulins are increased in serum and also excreted in urine causing cast nephropathy and AKI. Prompt diagnosis and treatment are crucial in such cases. Some other haematological diseases can also give rise to cast nephropathy like Waldenstrom macroglobulinaemia (lymphoplasmacytic lymphoma) and chronic lymphocytic leukaemia, in these conditions it is called as light chain nephropathy. In patients with MM other lesions like amyloid light chain (AL) amyloidosis or monoclonal immunoglobulin deposition disease (MIDD) can also occur. Diagnosis is based on bone marrow with more than 10% clonal plasma cells, free light chain assays, serum and urine protein electrophoresis and immunofixation. Renal biopsy is only required in selected number of cases of diagnostic uncertainty or for prognostic information about kidney outcome. The standard management regimen is triplet regimen based on bortezomib, cyclophosphamide and dexamethasone. However, recent studies suggested double regimen with bortezomib and dexamethasone to be as good as triple regimen.[3] Other steps in management include good hydration with parenteral fluids as much as tolerated, avoidance of NSAIDs, aminoglycosides, contrast agents, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and loop diuretics. Hypercalcaemia can be addressed with bisphosphonates. Autologous HSCT is advisable in selected cases when they achieve remission.

Lymphoma and chronic lymphocytic leukaemia

In patients with advanced non Hodgkin lymphoma about 63-90% develop lymphomatous infiltration of kidney.[4] Whereas in chronic lymphocytic leukaemia malignant cells are mostly in blood stream and in bone marrow and kidney infiltration is subclinical.[5] AKI due to direct infiltration usually occurs when infiltration is bilateral and diffuse and involves kidney interstitium, compression on tubules can cause tubular obstruction. Rarely a granulomatous reaction can give rise to acute granulomatous interstitial nephritis. Imaging reveals bilateral large size kidneys and diagnosis is confirmed by immunohistochemistry for B cell lineage. Timely introduction of chemotherapy generally results in rapid improvement in renal function and reduces kidney infiltration.

Thrombotic Microangiopathy (TMA)

TMA is also a cause of AKI in patients with haematological malignancies and can be caused directly from malignancy or related to drugs given for treatment. It can be classified according to endothelial cell injury mechanisms.[6] About 20 % patients with POEMS syndrome (polyneuropathy, endocrinopathy, organomegaly, monoclonal gammopathy and skin changes) develop TMA and kidney involvement.[7] As activity of ADAMTS 13 and complement factor H autoantibody are not well demonstrated in patients developing TMA with MM or lymphoma the exact mechanism of this phenomenon remain dubious. Therefore, role of targeted treatment with eculizumab remain unclear.

Treatment related AKI

CAR-T and immunotherapy can cause AKI via cytokine release syndrome mechanism, electrolyte imbalance and acute tubular injury occurs in this situation. The platinum

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compounds commonly used as chemotherapy for haematological malignancies are known nephrotoxins causing direct cellular damage, proximal tubular injury or TMA.

Tumour Lysis Syndrome

It is caused by rapid destruction of tumour cells which can be spontaneous or related to chemotherapy and is a medical emergency. The cell lysis results in hyperuricaemia, hypherphosphataemia, hyperkalaemia and hypocalcaemia. Thus crystal dependent or crystal independent both pathways can play a role. Treatment is aimed to increase urine output and lowering uric acid. Allopurinol is the commonly used agent, which prevents conversion of xanthine and hypoxanthine to uric acid.

HSCT associated AKI

AKI has been reported in up to 30-70% cases of HSCT.[8] Pre renal azotaemia is the most common cause of AKI in these patients, secondly these patients are at increased risk of sepsis which has different mechanisms of developing AKI. Pre-operative conditioning regimens also may carry nephrotoxic elements. Marrow transfusion toxicity can also cause AKI. Some other causes may include hepatic sinusoidal obstruction, infection with polyoma virus or adenovirus and graft versus host disease. Patients undergoing allogeneic HSCT with AL amyloidosis or POEMS syndrome may also develop engraftment syndrome resulting in AKI.[9] Prognosis of these patients worsens with development of AKI and mortality as high as 80-90% has been reported in patients where renal replacement was required.[10] Thus prompt identification and management is very important. Urinary alkalinisation and diuresis with mannitol are the main treatment for marrow transfusion toxicity.

Conclusion

AKI is common with haematological malignancies with diverse etiology and pathological mechanisms. A better understanding of these phenomena by both nephrologist and haem-oncologist is essential for managing such patients. A fine balancing between nephrotoxicity and use of life saving chemotherapeutic agents is important for the best outcome.

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