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CKJ REVIEW

Renal involvement in chronic lymphocytic leukemia

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most commonly diagnosed adult leukemia in the USA and Western Europe. Kidney disease can present in patients with CLL as a manifestation of the disease process such as acute kidney injury with infiltration or with a paraneoplastic glomerular disease or as a manifestation of extra renal obstruction and tumor lysis syndrome. In the current era of novel targeted therapies, kidney disease can also present as a complication of treatment. Tumor lysis syndrome associated with novel agents such as the B-cell lymphoma 2 inhibitor venetoclax and the monoclonal antibody obinutuzumab are important nephrotoxicities associated with these agents. Here we review the various forms of kidney diseases associated with CLL and its therapies.

Keywords: AKI, CLL, infiltration, leukemia, onconephrology, paraproteinemia, venetoclax

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most commonly diagnosed adult leukemia in the USA and Western Europe. Approximately 20 000 new CLL cases are expected to be diagnosed in the USA in 2017 [1]. The disease affects primarily the elderly, with the majority of patients being diagnosed at a relative older age (>65 years). The disease is usually monitored conservatively until disease-related symptoms develop. Most common manifestations of CLL that require initiation of therapy include fevers, night sweats, weight loss, organomegaly or lymphadenopathy causing discomfort and bone marrow failure (evidenced by worsening anemia or thrombocytopenia) [2, 3]. Unfortunately, by the time most patients require therapy, patients have acquired chronic comorbidities that limit their performance status and ability to tolerate therapy. Hence patients may become too frail to tolerate a regimen that may be associated with severe toxicities such as myelosuppression requiring transfusion support, life-threatening infections or severe organ damage.

Reports published between 1966 and 1973 constituted the basis on which Rai *et al.* [4] developed a system of staging of CLL that could prospectively distinguish patients according to their overall outlook for survival (Table 1). This method of staging was recognized as a simple, yet accurate prognostic tool for estimating survival and received wide acceptance by clinicians. In the current era, genetic and protein markers are also used to characterize CLL. Important characteristics of CLL cells are the presence of the immunoglobulin variable heavy chain (*IGHV*) gene repertoire and expression of stereotyped B-cell receptors [5, 6]. Approximately half of CLL clones will demonstrate unmutated immunoglobulin heavy chain variable regions, a finding associated with shorter overall survival and a higher risk of

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Table 1. Rai staging of CLL

Stage	Description	Median survival (months)	Risk status (modified Rai)
0	Lymphocytosis, lymphocytes in blood >15 000 lymphocytes/mm^3 and 40% lymphocytes in bone marrow	140	Low
I	Stage 0 with enlarged lymph node(s)	100	Intermediate
II	Stages 0–I with hepatomegaly, splenomegaly or both	70	Intermediate
III	Stages 0–II with hemoglobin <11 g/dL or hematocrit <33%	20	High
IV	Stages 0–III with platelets <100 000/μL	20	High

Adapted from the National Cancer Institute guidelines and Rai *et al.* [4].

relapse following chemoimmunotherapy. In addition, the presence of CD38 appears to be independently associated with an adverse prognosis [5, 6]. Zeta chain–associated protein 70 (ZAP70), a tyrosine kinase normally expressed by natural killer and T cells, is required for normal T-cell receptor signaling. ZAP70 is not normally expressed in B lymphocytes but has been found in a subset of patients with CLL and appears to correlate with survival [5, 6]. Specific cytogenetic abnormalities identified by fluorescence *in situ* hybridization (FISH) analysis and abnormalities in certain genes identified by molecular genetic testing confer prognostic significance in patients with CLL. Of these, del(13q) and trisomy 12 are favorable prognostic findings. Historically, patients with del(17p) or del(11q) have been at high risk of either not responding to initial treatment or relapsing soon after achieving remission [5, 6].

KIDNEY DISEASES WITH CLL

Kidney disease in patients with CLL may impact survival and occurs through diverse mechanisms such as leukemic infiltration, extrarenal obstruction, tumor lysis syndrome (TLS), glomerular diseases, electrolyte disorders and medication side effects. Here we review the kidney diseases associated with CLL and its treatments.

Strati and Shanafelt [7] found a 7.5% incidence of kidney disease at diagnosis in a cohort of >2000 patients with CLL at the Mayo Clinic. Renal insufficiency at baseline was associated with male gender, older age, more advanced disease and CLL CD49d positivity; these patients were less likely to receive purine nucleoside analogue therapy and were more likely to receive single alkylator-based therapy. Acute kidney injury (AKI) developed in 16% of patients during follow-up and was associated with older age, male gender and certain CLL characteristics (IGHV UM, CD49d$^+$, CD38$^+$, ZAP-70$^+$, del17p$^-$, or del11q$^-$) [7]. A study from the Mayo Clinic found that the presence of kidney disease is independently associated with adverse patient outcomes in CLL. Kidney disease at diagnosis of CLL or during follow-up had a significantly decreased overall survival compared with those without kidney disease [8]. Thus the presence of kidney disease in patients with CLL affects patient treatment strategies, clinical trial candidacy and outcomes. Due to the fact that CLL usually follows an indolent course, patients with CLL rarely undergo kidney biopsy. In the study by Strati *et al.* [8], of all the CLL patients studied, only 1.2% of patients underwent kidney biopsy. The low rate of kidney biopsy is a limiting factor in our understanding of CLL-associated kidney disease.

Table 2. Summary of various causes of kidney injury in patients with CLL

Type of etiology	Potential causes
Prerenal	Poor oral intake; sepsis and hypoperfusion; heart failure; cirrhosis; medications such as diuretics, non-steroidal anti-inflammatory agents, angiotensin receptor blockers and angiotensin-converting enzyme inhibitors
Intrinsic renal	Glomerular diseases TMA Acute tubular necrosis—sepsis, nephrotoxic agents and in some cases hyperviscosity and therapy agents Acute interstitial nephritis—infections such as BK or adenovirus, urinary tract infections, medication or chemotherapy induced or malignant cell infiltration
Postrenal	Obstruction from extrinsic compression of pelvacalcyceal system by tumor or lymph nodes TLS—uric acid nephropathy and intratubular obstruction from cancer itself or related to the use of CLL-directed therapy

AKI in CLL

AKI in patients with leukemia is common. A study looking at >300 patients with hematologic malignancies admitted to an intensive care unit demonstrated some form of AKI in >40% patients. Of those, 29% required renal replacement therapy, with an astounding mortality rate of 72%. The etiology of AKI that occurs in most hematologic malignancies, including CLL, are diverse [9]. One study of patients of all hematologic malignancies noted that the most common causes of AKI were hypoperfusion, TLS, hemophagocytic syndrome, direct infiltration of malignant cells and infections [10]. Another study found the most common cause of AKI in hematologic malignancies was prerenal azotemia [11]. Based on our experience, prerenal azotemia, acute tubular necrosis, TLS from chemotherapy agents and infiltrative disease are the common causes of AKI in CLL. Table 2 summarizes the etiologies causing AKI in patients with CLL.

Renal infiltration and obstruction

The infiltration of extramedullary organs can occur in CLL, but this complication is typically unusual. Postmortem retrospective series and case reports have demonstrated an infiltration of monoclonal B cells in the kidneys of patients that developed AKI before their demise. Autopsy studies show that ~60–90% of

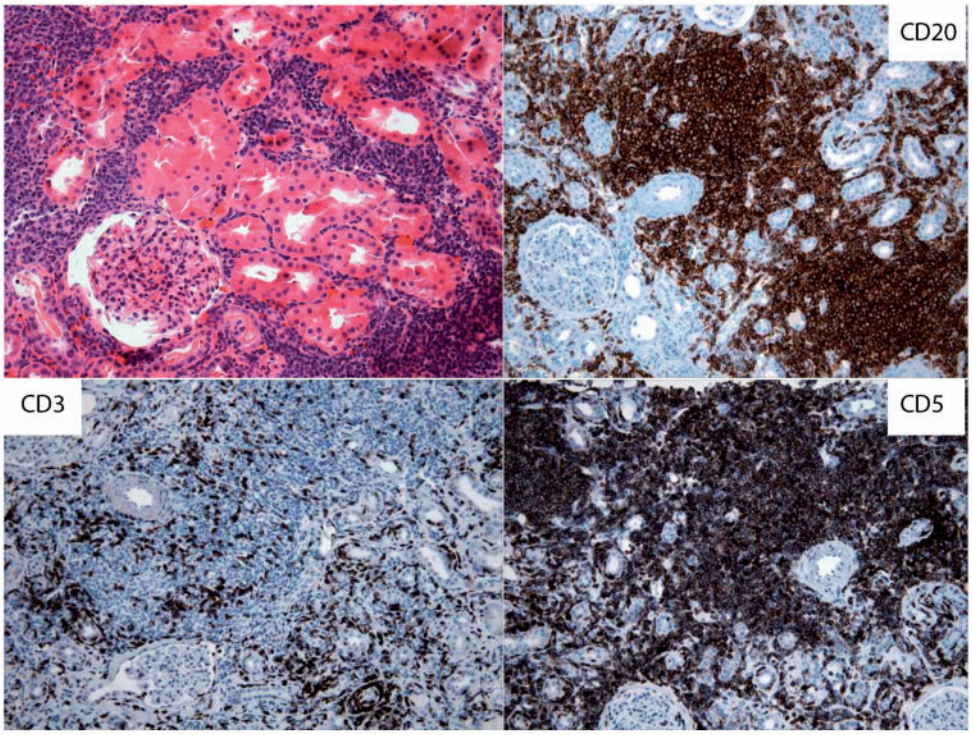

FIGURE 1: The renal parenchyma is infiltrated by monomorphic lymphocytes with an immunotype characteristic of CLL/small lymphocytic lymphoma. Immunohistochemistry stains reveal strongly positive B-cell marker CD20, negative T-cell marker CD3 and aberrantly expressed T-cell marker CD5.

patients may have leukemic-cell infiltration in the kidneys but, even at late stages, kidney function may remain unimpaired [12, 13]. This clinical phenotype has been linked to a more aggressive or advanced Rai stage. A retrospective study by Poitou-Verkinder *et al*. [14] identified 15 patients afflicted with CLL from a repository of 3950 kidney biopsies. Pathology showed that CLL monoclonal infiltrates were present in 10 of the biopsies; 9 patients had glomerulopathies, with membranoproliferative glomerulonephritis (MPGN) being the most commonly reported histologic form. A large Mayo Clinic study that included patients with both CLL and monoclonal B-cell lymphocytosis had a kidney biopsy if they presented with nephrotic syndrome or renal insufficiency. Of 4012 patients with CLL, only 49 (1.2% of all patients) had pathological findings of CLL (infiltration and glomerular diseases) in their kidneys [8]. This is in striking contrast to autopsy studies done in the 1980s [12, 13]. Interestingly, the pattern or extent of infiltration did not correlate with the degree of AKI [8]. Another review of the literature found 17 reports of patients with kidney biopsies showing renal infiltration by CLL in addition to other histologic findings, with no association found between the absolute lymphocyte count and CLL renal infiltration [15]. Kidney function has been noted to improve with CLL treatment in many patients with infiltrative disease on biopsy [14]. Figure 1 shows a case of AKI with CLL infiltrative disease.

The mechanism of AKI with CLL infiltration is not clearly established but has been hypothesized to involve tubular/microvascular compression causing intrarenal obstruction in addition to an infiltration-associated inflammatory/cytokine response [12, 16]. The radiology literature also describes the use of multidetector row computed tomography (CT), magnetic resonance imaging (MRI), positive emission tomography and ultrasound to identify CLL involvement of the kidney, but these studies do not include histologic correlation. In general, when kidney involvement is detected at imaging, there is also evidence of extramedullary involvement in other sites. The most common imaging pattern of kidney involvement in leukemia is nephromegaly, which can affect one or both kidneys and results from diffuse or nodular parenchymal infiltration by leukemic cells [17, 18]. The sensitivity and specificity of this finding are not known. For example, one series found that only 1 of 10 patients with biopsy-proven renal infiltration had increased kidney size [14]. Other abnormalities include single or multiple nodules and wedge-shaped or geographic areas that enhance less than the adjacent normal renal parenchyma after intravenous contrast agent administration [17, 18]. No specific studies have investigated how changes in imaging correlate as kidney function improves or worsens with CLL.

Obstructive nephropathy in the setting of CLL can be observed and is diagnosed radiographically via ultrasound, MRI or CT scan. Bilateral hydronephrosis from obstructing nodes is managed with decompression and treating the underlying CLL [16].

Other interstitial diseases

Granulomatous interstitial nephritis (non-infection related) in the setting of CLL has been described in case reports and small case series [19], with partial recovery in 90% of the patients with CLL treatment. BK virus nephropathy in the native kidneys has also been reported with CLL [15, 20].

Glomerular diseases

Several glomerular diseases have been associated with CLL, with >50 cases mentioned via case reports and case series. The most frequently reported findings are MPGN (36%) and membranous nephropathy (19%). While specific percentages are not

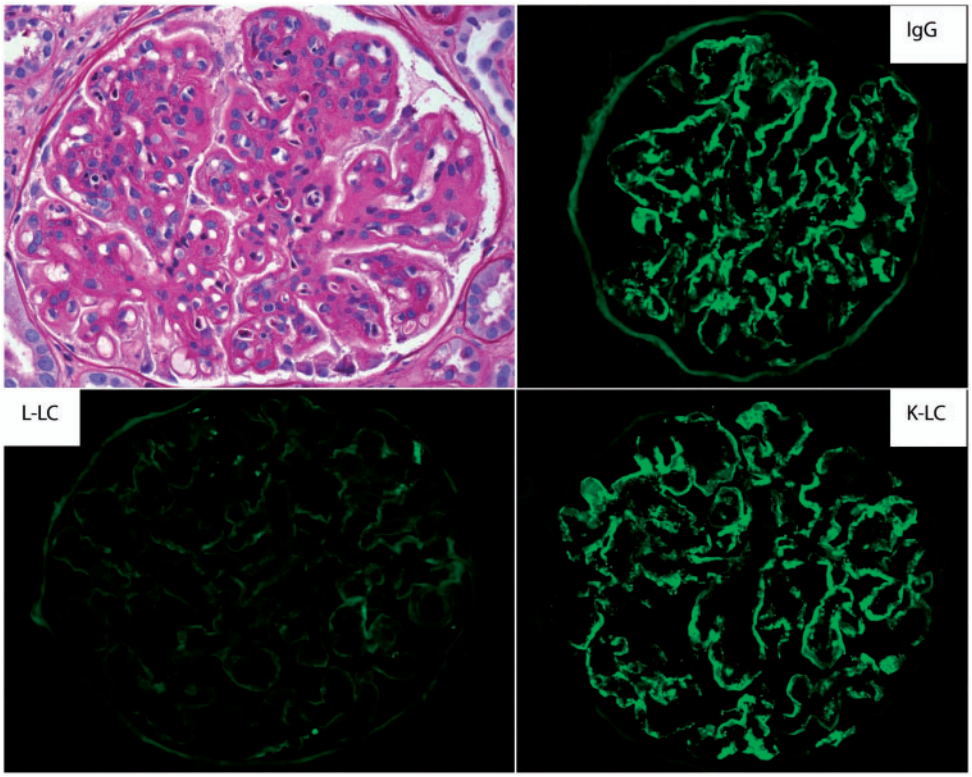

FIGURE 2: A glomerulus with a membranoproliferative pattern of injury. There is marked mesangial expansion by matrix and cells, thickened and remodeled capillary walls and frequent inflammatory cells in the glomerular capillary lumens. By immunofluorescence microscopy, this lesion reveals IgG-kappa restricted reactivity. Lambda light chain is completely negative.

available, a large number of cases exist of CLL with amyloidosis as well. Other rare findings are minimal change disease (MCD), immunotactoid glomerulopathy and focal segmental glomerulosclerosis [8, 14].

Paraprotein-mediated kidney disease has been well described in CLL, ranging from 2.5 to 60% of cases [8]. In a study from France, 6/15 patients that underwent a kidney biopsy in a CLL cohort presented with a monoclonal dysproteinemia [14]. Abnormal serum free light chains can be detected in ~30–40% patients with CLL. Recent data suggest a significant correlation between the abnormal free light chain ratio and outcome of CLL patients [21]. The monoclonal protein secreted by the B-cell clone can either be directly involved in the pathogenesis of the lesions, as in cases of fibrillary glomerulopathy, immunotactoid nephropathy, amyloid light chain (AL) amyloidosis or type I/II cyroglobulinemia or indirectly in cases of MPGN not related to cyroglobulinemia [14]. Light chain cast nephropathy has also been described in patients with CLL [8].

By far the most common glomerular lesion noted in CLL patients is MPGN (Figure 2). In most studies the majority of the patients had a paraproteinemia [8, 14]. Cryoglobulin-associated MPGN was also fairly common in this subgroup [8]. In cases of fibrillary and immunotactoid glomerular diseases seen in CLL, light microscopy findings were suggestive of MPGN, with many patients having a circulating monoclonal protein (Figure 3). Cases of MPGN presenting as C3 glomerulonephritis have also been reported, suggesting indirect damage via activation of the alternative complement system [22].

MCD has also been reported in many cases of CLL [8, 11]. The pathophysiology of this association is unclear. Both a B-cell-mediated mechanism and T-cell dysfunction have been proposed. The co-development of a podocytopathy along with hematologic malignancy and resolution of the glomerular diseases with chemotherapy strongly suggests an immune-mediated mechanism. Interestingly, MCD was described in a patient with monoclonal B lymphocytosis; a precursor state of CLL [23]. Similar to monoclonal gammopathy of unclear significance that can lead to kidney disease, monoclonal B lymphocytosis can also be responsible for kidney disease [24].

Membranous nephropathy is usually more common with solid tumors [25]. CLL-associated membranous nephropathy has been described and a few of them respond to chemotherapy of CLL [8]. The cases described were prior to the discovery of the M-type phospholipase A2 receptor on podocytes that has been associated with primary membranous nephropathy [26].

Systemic amyloidosis has been associated with CLL. A large study from the Mayo Clinic reviewed all cases of CLL and amyloidosis [27]. Over a span of 20 years, 33 patients were identified, 61% had AL amyloidosis and 39% had non-AL amyloidosis. Of the 18 patients with AL amyloidosis that had typing results available, four had a CLL clone only and the remaining 14 had both a plasma cell and CLL clone. Six patients had both a plasma cell and CLL clone that shared the same light chain. For patients with AL amyloidosis associated with CLL, the patients received agents that targeted B and plasma cells. The median survival for AL amyloidosis patients with CLL was 38.9 months [27]. Other sporadic cases of AL amyloidosis have been reported with CLL and treatment is challenging, as it is not easy to decipher if the CLL and plasma cell dyscrasias are truly related or two separate entities [28–33].

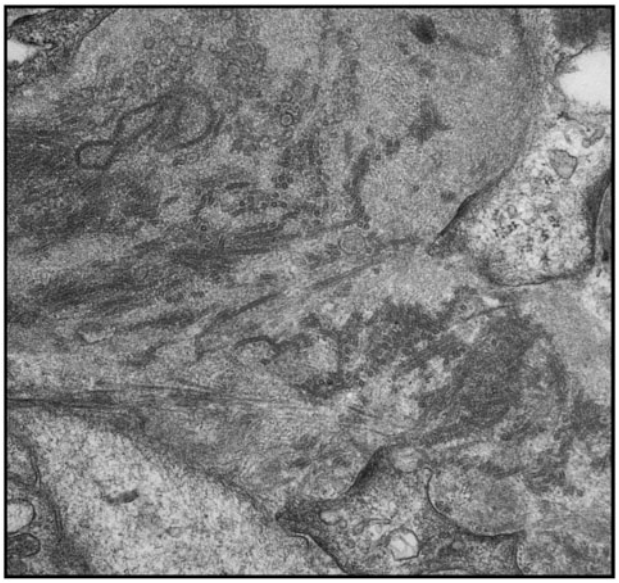

FIGURE 3: Immunotactoid organized deposits within the mesangial matrix. The deposits are composed of microtubules, sometimes in a parallel arrangement.

Nine patients in the above-mentioned cohort [27] had non-AL amyloidosis. Cases with non-AL amyloidosis that had amyloid typing done comprised mostly the patients with the transthyretin (seven patients) form of amyloidosis. One patient had insulin-type amyloid and she was a type 1 diabetic who had been on insulin for >50 years prior to diagnosis of amyloidosis [27]. The patients with non-AL amyloidosis with CLL received no specific agents targeting plasma cell clones. The median overall survival of the non-AL amyloidosis patients was 61.4 months, much better than the AL amyloidosis patients with CLL [27].

The high prevalence of an abnormal serum free light chain ratio and increase in free light chains in general in patients with CLL brings into question whether a subset of these patients with CLL have undiagnosed AL amyloidosis [22]. Polyclonal B cells share the same microenvironmental interactions as tumor cells and could themselves be activated by antigenic stimulation of the CLL clone. This later may in turn convey activatory signals to bystander B and T lymphocytes. It is possible that the tumor-derived monoclonal free light chains can be admixed with variable amounts of serum free light chains produced by non-clonal bystander B cells in the lymphohematopoietic tissues [22].

Thrombotic microangiopathy (TMA) has been reported in patients with CLL. In the study by Strati *et al.* [8], six patients presented with TMA (renal limited or systemic) as the renal manifestation of CLL. Four of the six patients responded to treatment with CLL, one required a stem cell transplantation and the other had simultaneous lung cancer [8]. All six patients had clinical presentation of AKI, proteinuria, hemolysis, anemia, elevated lactate dehydrogenase and presence of schistocytes on peripheral smear and low haptoglobin. Other associated glomerular diseases with CLL are listed below in Table 3 in order of incidence.

Glomerular diseases associated with cancer, and in this case CLL, can present preceding the CLL diagnosis [25]. CLL is frequently not treated or treated late. If there is end organ damage and we are able to connect the kidney disease to CLL, perhaps treatment might be important and critical for renal survival. The term 'CLL with renal significance' should be considered for cases that present with this dilemma.

Table 3. Summary of published cases of various glomerular diseases seen with CLL

Kidney pathology reported	Cases, *n*	Reference
MPGN[a]	37	[8, 14]
AL amyloidosis	24	[27–33]
MCD	13	[8, 11, 23]
Membranous nephropathy	12	[8]
AA amyloidosis	9	[27]
Proliferative GN	8	[8, 14]
Thrombotic microangiopathy	6	[8]
Fibrillary GN	4	[8, 14]
Immunotactoid glomerulopathy	4	[8, 14]
C3 GN	3	[22]
FSGS	2	[8, 14]

[a]Most cases included direct deposition of monoclonal proteins in the form of proliferative glomerulonephritis, C3 deposits or cryoglobulinemia.
AA, amyloid type A protein; GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis.

ELECTROLYTE DISORDERS

TLS

TLS is the most common oncologic emergency with an incidence as high as 26% in high-grade B-cell acute lymphoblastic leukemia [34]. TLS results from rapid release of the intracellular contents of dying cancer cells into the bloodstream either spontaneously or in response to cancer therapy. It is biochemically characterized by hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. Cardiac arrhythmias, seizures and superimposed AKI are common clinical presentations (Figure 4). Table 4 summarizes the Cairo–Bishop definition of laboratory TLS and clinical TLS. This is the classic definition used in diagnosing TLS. The pathophysiology of TLS-mediated AKI involves intratubular obstruction and inflammation by precipitation of crystals of uric acid, calcium phosphate and/or xanthine. Preexisting kidney dysfunction favors intratubular crystal precipitation. Consensus recommendations for TLS prophylaxis include volume expansion for all risk groups, use of allopurinol in medium- and high-risk groups and use of recombinant urate oxidase (rasburicase) in high-risk groups. The utility of diuretics and urine alkalization are variable and their efficacy is debatable [34, 35].

While TLS is uncommon in CLL, it is still an issue that needs to be addressed, particularly with the use of one of the novel targeted agents used in the treatment of CLL, namely the drug venetoclax. The use of venetoclax, a recently approved B-cell lymphoma 2 protein (bcl-2) inhibitor for use in a select group of patients with relapsed CLL that carry del17p (high risk of progression), has led to drug-induced TLS in 3–6% of patients [36]. In order to minimize the risk of TLS, a strict protocol has been established that will be discussed in more detail in a later section.

Other electrolyte disorders

The most common electrolyte disorder encountered in CLL patients is pseudohyperkalemia. Potassium tends to stay predominantly in the intracellular compartment. Leakage of

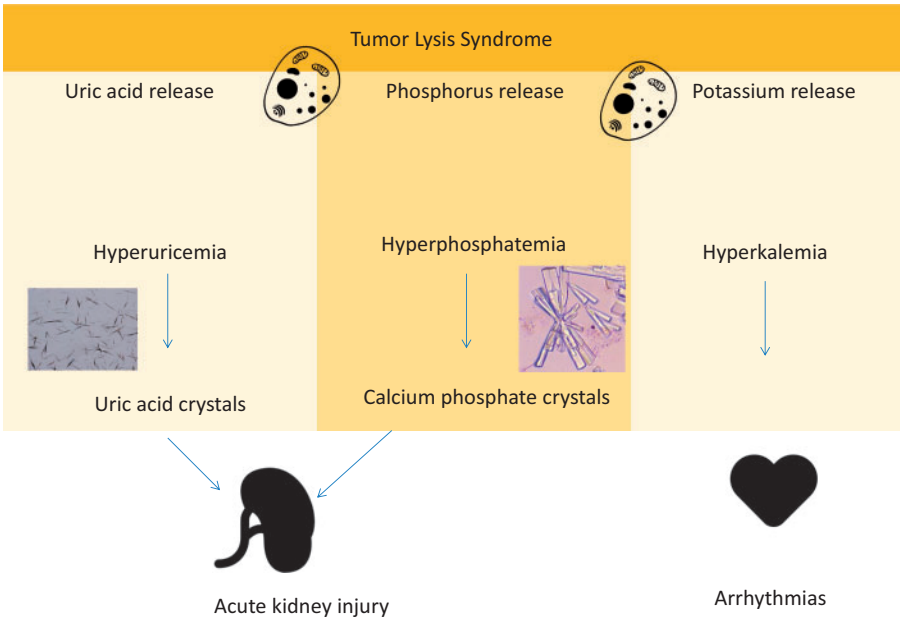

FIGURE 4: Clinical presentation summary of tumor lysis syndrome.

Table 4. Cairo–Bishop definition of laboratory TLS and clinical TLS

Electrolyte disorder	Criterion
Potassium	≥6 mEq/L or 25% increase from baseline
Phosphorus	≥4.5 mg/dL or 25% increase from baseline
Calcium	>25% decrease from baseline
Uric acid	≥8 mg/dL or 25% increase from baseline

Clinical criteria: laboratory criteria and one or more of the following: (i) creatinine × ≥1.5 upper limit of normal, (ii) seizures, (iii) cardiac arrhythmia or sudden death. Laboratory TLS requires that two or more of the following metabolic abnormalities occur within 3 days before or up to 7 days after the initiation of therapy: hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. Clinical TLS is present when laboratory TLS is accompanied by an increased creatinine level, seizures, cardiac dysrhythmia or death.

potassium from the intracellular compartment at the time of collection due to hemolysis, cell fragility or heparin-induced damage can lead to spurious elevation of measured potassium levels, which is known as pseudohyperkalemia. In addition, myeloproliferative disorders and thrombocytosis can also lead to pseudohyperkalemia. Thrombocytosis (platelet count >1000 × 10^9/L) can also lead to pseudohyperkalemia. Elevation of the blood platelet count by 1000 × 10^9/L can lead to an increase of 0.2 mmol/L in plasma potassium and 0.7 mmol/L in serum potassium [37]. As a result, the potassium concentration is generally higher in serum compared with plasma from platelets during clotting. Similarly, elevated potassium levels have been described in leukocytosis as well. An artifactually elevated serum potassium level or spurious hyperkalemia was first described [38] with extreme leukocytosis (>600 × 10^9/L) and several case reports thereafter [39–41]. Katkish *et al.* [42] reviewed >300 patients with CLL listed in the tumor registry in the state of Minnesota between 1997 and 2014. The researchers found that the adjusted odds of a patient's potassium being elevated increased by 1.4 [95% confidence interval (CI) 1.2–1.5; $P < 0.0001$] for every 10 × 10^9/L increase in white blood cell count. Below a white blood cell count of 50 × 10^9cells/L, the median estimated percentage of a patient's potassium being elevated was 1.7%, but was considerably higher, at 8.1%, when the white blood cell count was ≥100 × 10^9/L. This is the first and only study to systematically look at serum potassium values in CLL patients [42] demonstrating that the results are related to pseudohyperkalemia.

Routine serum analysis leads to high measured potassium levels due to the release of potassium from fragile leukemic cells during the clotting process. But in CLL, even the plasma levels of potassium are elevated. Severe leukocytosis leads to consumption of metabolic fuels that can impair sodium-potassium ATPase activity, leading to release of potassium from a high number of white cells [43]. While in elevated platelet levels, serum and plasma levels can differentiate pseudohyperkalemia, elevated white cell–related pseudohyperkalemia might not be as straightforward to distinguish. While not common, another interesting electrolyte disorder noted in CLL patients is reverse pseudohyperkalemia [44, 45], where plasma potassium is noted to be higher than serum potassium [46]. The mechanism is not well understood but may be due to an increase in sensitivity to heparin-mediated cell membrane damage during processing and centrifugation in a hematologic malignancy and mechanical stressors. To our knowledge, there is no specific way to predict or correct the measured potassium value based on the white cell count.

The time to collection and analysis of the blood sample can help eliminate some of these findings. Allowing serum to sit on the clot for too long (>2 h) can significantly increase the potassium values. Ideally, specimens for patients with significantly elevated white cell counts should be delivered in person to minimize hemolysis. Arterial blood gas samples in a balanced heparin syringe for potassium measurement can decrease the transit time to allow for more accurate potassium measurement. Venous blood gas measurements can be useful, but keep in mind that venous samples have more mechanical stressors compared with arterial blood draw techniques, making arterial draws more accurate. We also recommend checking a simultaneous plasma potassium level in patients with white cell counts >100 × 10^9/L. An electrocardiogram (EKG) can be helpful in differentiating pseudohyperkalemia/reverse pseudohyperkalemia from true hyperkalemia. The absence of typical EKG changes is

Table 5. Summary of FDA adverse events by targeted agents used in CLL (2014–17)

Agent	AKI	Hyponatremia	Hypokalemia	Hypophosphatemia	Hypomagnesemia	Hyperkalemia	Proteinuria	TLS	Total
Alemtuzumab	**25**	0	0	0	0	0	3	1	33
Ofatumumab	**29**	7	6	0	0	3	0	**16**	61
Ibrutinib	9	**9**	5	4	1	3	0	6	37
Idelalisib	4	1	2	0	0	3	0	8	18
Obinutuzumab	10	0	0	1	0	1	0	8	20
Venetoclax	0	4	0	0	0	0	0	2	6

Bold numbers suggest highest type of injury.

usually helpful in identifying pseudohyperkalemia. High plasma lactate dehydrogenase levels may indicate hemolysis or rupture of fragile white blood cells seen in CLL patients. Consideration should be given to testing serum potassium if the plasma potassium is elevated in the context of leukocytosis, especially if reverse pseudohyperkalemia is suspected. In addition, we suggest placing a warning in the electronic medical record to alert clinicians to potential pseudohyperkalemia in patients with CLL and leukocytosis. Such recognition might help prevent costly and harmful emergent dialysis, intravenous calcium or insulin and cancellation of procedures.

Hypercalcemia in CLL is extremely rare but ∼30 cases have been reported [47–49]. In a retrospective study of 1200 patients with CLL, 7 patients had high calcium levels [50]. Proposed mechanisms causing hypercalcemia in CLL patients are parathyroid hormone–related peptide and 1,25 vitamin D mediated (similar to B-cell lymphomas). Hypercalcemia should also raise concern for a potential CLL transformation to a large-cell lymphoma or another form of aggressive lymphoma [51]. Other various electrolyte disorders that present in CLL are usually treatment related and are discussed below.

TREATMENT-RELATED TOXICITIES

The current standard of care for a fit patient with CLL without comorbidities is a chemo-immunotherapeutic regimen that includes the purine analog fludarabine in combination with cyclophosphamide and rituximab [52]. However, this combination regimen remains toxic for the majority of patients with CLL due to age and comorbidities, particularly due to increased risk for infectious complications [53]. Over the last few years, treatment of CLL has slowly started to evolve from regimens with significant impact on long-term outcomes and associated concomitant toxicities to the use of novel agents that specifically target dysregulated pathways. These advances are possible given our recent understanding of CLL biology, mainly elucidation of the role of the microenvironment and of the signaling mechanisms that allow for survival and proliferation of the malignant CLL clone. These targeted agents include the monoclonal antibody obinutuzumab, the Bruton's tyrosine kinase inhibitors ibrutinib and acalabrutinib, the phosphatidylinositol 3-kinase inhibitor idelalisib and the BCL-2 inhibitor venetoclax [54–58]. These novel agents are demonstrating unprecedented clinical activity, especially in patients with historically low response rates, such as patients with high-risk disease (unmutated *IGHV*). Since these drugs are relatively new, we are still learning about their potential renal toxicities.

Most medications used for the treatment of CLL are not nephrotoxic. While fludarabine has been associated with a few case reports of glomerular disease [59], this is not a common finding. Ibrutinib [60] and venetoclax [58] have been associated with elevated serum creatinine. In addition to reviewing the published literature, we also reviewed the US Food and Drug Administration (FDA) adverse event reporting system (FAERS) quarterly legacy data file (third quarter of 2014 to second quarter of 2017) for all recently approved targeted agents for CLL. Well-established chemotherapy agents used in CLL such as cyclophosphamide and fludarabine were excluded. The adverse event terms queried were hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypocalcemia, hypercalcemia, hyperkalemia, hypernatremia, hyperphosphatemia, proteinuria, renal failure acute, AKI, TLS, hypertension and nephritis. We reviewed the literature using MEDLINE, case series and the registration studies of these agents for any reported nephrotoxicity. Table 5 summarizes the drugs studied and results found. Ofatumumab, alemtuzumab and ibrutinib were the top three offenders, with AKI as the most common finding reported, followed by TLS and hyponatremia. The newer agents used to treat CLL had fewer renal toxicities than the older agents. Given that some of the newer agents (such as obinutuzumab and venetoclax) are not yet widely used, the true rate of renal toxicities may be underestimated. The mechanism of AKI is unclear in most of these agents. TLS has been rarely reported in patients treated with ibrutinib and acute interstitial nephritis (unpublished, personal communication) has been observed while on ibrutinib. In addition, in the largest unpublished series focused on hypertension in ibrutinib-treated patients, a clear association between ibrutinib and hypertension was noted [61]. Nearly 40% of patients developed hypertension within 12 months of exposure. Despite aggressive management (multiple agents), ibrutinib-associated hypertension was persistent [61]. The data underscore the critical need for monitoring and management strategies for hypertension and follow-up data on renal and cardiac events. The literature reviewed in the FAERS reported additional toxicities of the newer agents, such as TLS with venetoclax, leading to early modifications of the dose escalation protocol for the drug. The importance of following a strict ramp-up dosing protocol cannot be emphasized enough. The literature review of published case reports and series of all agents used in CLL are summarized in Table 6.

Venetoclax and TLS: an example

Venetoclax is now approved for patients with CLL that harbor the chromosome 17p deletion (high risk of progression) who have received at least one prior treatment and for whom there are no other available therapies [58]. The drug is currently being reviewed by the FDA for wider approval in patients with relapsed CLL. This is based on the results presented at the annual American Society of Hematology meeting of the MURANO trial, where venetoclax was used in combination with rituximab in relapsed/refractory patients with CLL [76]. In the initial Phase

Table 6. Adverse events with CLL therapies

Drug	Mechanism of action	Commonly published renal adverse events	Comments
Alemtuzumab	Anti-CD52 monoclonal antibody	Antiglomerular basement membrane disease, AKI	Used in kidney transplants without significant renal effects
Acalabrutinib	Bruton's tyrosine kinase inhibitor	Increased creatinine	Recent approval in 2017, unclear if it has any significant kidney toxicity
Bendamustine	Nitrogen mustard	Hypokalemia, hyponatremia and hypocalcemia	
Chlorambucil	Alkylating agent	Hyponatremia (SIADH)	
Cyclophosphamide	Alkylating agent	Hemorrhagic cystitis, urinary fibrosis and retention, SIADH	
Dinaciclib	CDK9 inhibitor	TLS	3–15% (three cases thus far of TLS)
Favopiridol	CDK9 inhibitor	TLS	25% TLS in initial trials—all of the first five trials patients had TLS, two deaths, several cases of dialysis and hospitalizations
Fludarabine	Purine analog	Hematuria, proteinuria and TLS	
Ibrutinib	Bruton's tyrosine kinase inhibitor	AKI, hypertension, hypophosphatemia and hyponatremia	The TLS mentioned in the literature in initial trials has not been reported postmarketing
Idelalisib	P13K inhibitor	Hypokalemia, AKI and hyponatremia	
Lenalidomide	Immunomodulator	TLS, hypokalemia, Fanconi syndrome, AKI (biopsy proven acute interstitial nephritis)	Trial amended after TLS onset in 4 of the first 18 patients (2.9%)
Obinutuzumab	Anti-CD20 monoclonal antibody	TLS, hypophosphatemia, hypocalcemia, hyperkalemia and hyponatremia AKI	2–4.5% TLS; all cases resolved in initial trials
Ofatumumab	Anti-CD20 monoclonal antibody	TLS, AKI	3–4% TLS; all cases resolved in initial trials
Rituximab	Anti-CD20 monoclonal antibody	TLS	In Phases II and III trials, <1% TLS
Venetoclax	BCL-2 inhibitor	TLS	Six patients with clinical TLS including two deaths during dose escalation and many clinical and laboratory TLS cases

Based on references [54–79] and the FDA adverse reporting system.
AKI, acute kidney injury; BTK, Bruton tyrosine kinase; CDK, cyclin-dependent kinase; P13K, phosphatidylinositol 3-kinase; SAIDH, syndrome of inappropriate antidiuretic hormone.

1 trial ($n = 56$) of this agent, three patients experienced clinical TLS and seven had clinical parameters of TLS despite slow increments in dosing (venetoclax initiated at 50 mg and ramped up to a maximum target dose of 1200 mg over 3 weeks) and TLS prophylaxis [55]. Of the three patients, one died due to severe hyperkalemia and one required immediate dialysis. Clinical TLS occurred in two patients (resulting in one death) who initiated venetoclax at 50 mg in the Phase Ib trial that was used as the basis for the MURANO trial [77].

Based on this experience, a slow ramping of venetoclax was started with initial doses starting at 20 mg for 1 week, followed by a ramp-up scheme totaling 5 weeks to a target dose of 400 mg along with intensive TLS prophylaxis and monitoring in real time (Figure 5). A data review of reports of TLS with this agent revealed that a combination of tumor burden (bulky lymph nodes ≥5 cm and or elevated lymphocyte count $\geq 25 \times 10^9$) and reduced renal function at screening could be used to identify high-risk patients that might develop TLS [78]. For moderate- to high-risk patients, and especially with a creatinine clearance <80 cc/min, the initial 20 and 50 mg doses should be administered in the hospital with laboratory monitoring at specified timepoints (after 4, 8, 12 and 24 h), early prophylaxis with allopurinol or rasburicase and aggressive intravenous fluids. Phosphate measurement might be the earliest clue to tumor lysis and should prompt nephrology consultation before severe TLS ensues [79]. With the new dosing regimen and close monitoring guidelines appropriate for the level of risk of TLS, TLS has become a less common occurrence. At our center, the nephrology and intensive care unit teams are made aware of any admission where venetoclax is planned to be administered and dose-escalated in patients with CLL. We have performed early

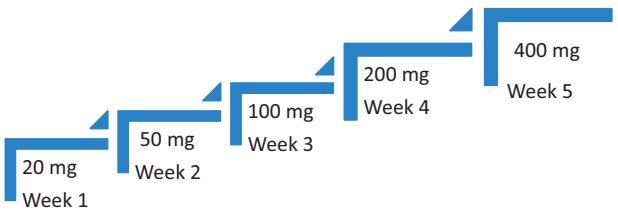

FIGURE 5: Recommended once-daily dosing schedule for venetoclax 5-week dose ramp-up used in clinical trials of patients with CLL. For patients with high tumor lysis risk (any measurable lymph nodes with largest diameter >10 cm or absolute lymphocyte count $>25 \times 10^9$/L and any measurable lymph node with largest diameter >5cm), then the first doses of 20 mg and 50 mg should be inpatient dosing and lab monitoring done at 0, 4, 8, 12 and 24 h. Hydration with 1-2 L/day of fluids with rasburicase recommended. Early Nephrology consultation in certain very high risk situations.

continuous renal replacement therapy in high-risk cases to allow for safe dose escalation of this agent. Nephrologists need to be aware of the potential toxicity of this CLL agent. Our recommendation is that early nephrology consultation might be prudent in most cases of moderate to severe risk of TLS with every dose escalation of venetoclax, in particular the first two dose escalations.

In addition to the possibility of CLL affecting the kidney, it is important to recognize that the risk of therapy-induced nephropathy increases with age. In a disease with prolonged survival, such as CLL, long-term toxicity becomes equally important, as the selected therapy may contribute to morbidity and mortality.

CONCLUSION

CLL can affect the kidney in various ways from infiltration, glomerular diseases and electrolyte disorders and indirectly with treatment-related toxicities. Because we are now in an era of more effective targeted therapies for CLL, TLS must be a consideration and proper prophylactic measures instituted. While CLL-associated kidney disease may occur due to multiple disease-related factors, treatment-associated AKI and TLS might be more important in this era of targeted therapies. The venetoclax clinical development program provides an example where collaborative management between various medical specialties can lead to mitigation of the TLS risk and complications related to a known potentially fatal toxicity. Familiarity with renal toxicities of CLL is important for hematologists and nephrologists in clinical practice.

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CONFLICT OF INTEREST STATEMENT

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