KDIGO Controversies Conference on onco-nephrology: kidney disease in hematological malignancies and the burden of cancer after kidney transplantation

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The bidirectional relationship between cancer and chronic kidney disease (CKD) is complex. Patients with cancer, particularly those with hematological malignancies such as multiple myeloma and lymphoma, are at increased risk of developing acute kidney injury and CKD. On the other hand, emerging evidence from large observational registry analyses have consistently shown that cancer risk is increased by at least 2- to 3-fold in kidney transplant recipients, and the observed increased risk occurs not only in those who have received kidney transplants but also in those on dialysis and with mild- to moderate-stage CKD. The interactions between cancer and CKD have raised major therapeutic and clinical challenges in the management of these patients. Given the magnitude of the problem and uncertainties, and current controversies within the existing evidence, Kidney Disease: Improving Global Outcomes (KDIGO) assembled a global panel of multidisciplinary clinical and scientific expertise for a controversies conference on onco-nephrology to identify key management issues in nephrology relevant to patients with malignancy. This report covers the discussed controversies in kidney disease in hematological malignancies, as well as cancer after kidney transplantation. An overview of future research priorities is also discussed.

Kidney International (2020) **98,** 1407–1418; https://doi.org/10.1016/j.kint.2020.07.012

KEYWORDS: chemotherapy; chronic kidney disease; kidney transplantation; oncology; tumor lysis syndrome

Cancer is becoming recognized as a major complication in patients with chronic kidney disease (CKD). The magnitude of the increased risk varies based on CKD severity, with the greatest risk among kidney transplant recipients. Convincing evidence from longitudinal observational analyses has suggested the excess risk of cancer and cancer-related death in kidney transplant recipients is at least 2-fold greater than the sex- and age-matched general population.[1,2] Specifically, the excess risk of viral-related cancers such as lymphoproliferative disease and Kaposi sarcoma is more than 10-fold.[1] Hematological or oncological malignancy is also associated with a plethora of kidney problems, such as CKD, acute kidney injury (AKI), electrolyte disturbances, glomerulonephritis, and thrombotic thrombocytopenic purpura. Both CKD and AKI can be caused either by processes related to malignancy or treatments for it.[3]

In patients with hematological malignancies, CKD can result from direct injury by cancer cells or indirect injury via

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Received 14 December 2019; revised 2 June 2020; accepted 2 July 2020

Table 1 | Research priorities for kidney disease in hematological malignancies

	Research priorities
Tumor lysis syndrome	• Define the optimal dosing of xanthine oxide inhibitors for preventing tumor lysis syndrome and define the target level of uric acid • Increase the knowledge base on the role of phosphorous and xanthine in tumor lysis syndrome • Evaluate how febuxostat compares with allopurinol in onset of action, effectiveness in lowering uric acid, and safety in the medium and long-term[14]
Multiple myeloma	• Explore whether therapeutic plasma exchange improves kidney or overall outcomes in multiple myeloma patients with high serum free light chain levels ○ Determine whether there is a threshold level for serum free light chains • Investigate combining efficient free light chain removal techniques with effective but tolerable chemotherapy[15] • Examine whether bisphosphonate is associated with adverse risks (thrombotic microangiopathy, nephrotic syndrome) in hemodialysis and peritoneal dialysis with multiple myeloma
Cast nephropathy	• Investigate biomarkers for predicting risk of cast nephropathy
MGRS	• Determine whether clonal deposits in the kidney are sufficient cause to start treatment ○ Develop a registry to help determine the number needed to harm vs. the number needed to treat • Determine the percentage of light chain staining in kidney biopsies • Determine how (and whether) to find the clone as a target of chemotherapy
KT in patients with myeloma and amyloidosis on dialysis	• Determine the optimal duration of remission of myeloma and amyloidosis prior to transplantation • Develop a registry of transplant patients to determine the following: ○ How to diagnose extrarenal organ dysfunction of amyloid ○ Whether there is a benefit of parallel bone marrow transplantation and kidney transplantation ○ Whether it is possible to expand the kidney donor pool
Dosing cytotoxic agents in CKD G3b–G5D	• Conduct postmarketing studies to generate data on dosing in CKD G3b–G5D • Investigate whether there is a clinically relevant difference between dosing based on creatinine clearance vs. eGFR • Determine how the dialysis session should be adapted for drug administration • Explore whether there are specific preventive strategies to avoid renal toxicity of cytotoxic agents or calcineurin inhibitors[16]
Novel sorbent devices in hematology/oncology	• Determine whether adsorbent devices offer a benefit over anti–IL-6 therapy approaches • Determine whether there is an indication for using new adsorbent devices in the setting of AKI stage 3 with need for kidney replacement therapy
ESAs in hematological cancer and CKD patients	• Generate data on safety of ESAs in CKD patients with hematological cancer • Determine target hemoglobin levels in CKD patients with hematological cancer • Evaluate newer oral ESAs in CKD patients with hematological cancer

AKI, acute kidney injury; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; eGFR, estimated glomerular filtration rate; IL, interleukin; KT, kidney transplantation; MGRS, monoclonal gammopathy of renal significance.

immunologically mediated mechanisms, such as occurs with membranous nephropathy.[4] AKI in patients with malignancy can be caused by lymphomatous infiltration of the kidneys, cast nephropathy in multiple myeloma and monoclonal gammopathies, and tumor lysis syndrome (TLS), and these occur mainly in malignancies with high tumor burden and rapid cell turnover.[4–6] In patients treated with hematopoietic cell transplantation, there are several unique causes of both AKI and CKD.[7] The risk of AKI can be potentiated by several factors: dehydration due to vomiting, diarrhea, obstruction of the urinary tract, fluid and electrolyte disturbances, contrast agent administration, nonsteroidal anti-inflammatory drugs, nephrotoxic antibiotics, and renal toxicity of chemotherapeutic or targeted drugs.[4–6] The incidence of AKI in patients with high-grade hematological malignancy has been estimated to be as high as 68.5% using RIFLE criteria (*r*isk, *i*njury, *f*ailure, *l*oss of function, *e*nd-stage kidney disease [ESKD]), with >90% of cases resulting from hypoperfusion, acute tubular necrosis, TLS, nephrotoxins, or hemophagocytic lymphohistiocytosis.[8]

Improved cancer outcomes through better diagnostics and personalized therapies such as selective genome- and immune-targeted drugs have resulted in a growing population of cancer survivors[9] who are at increased risk for kidney disease. Caring for oncology patients has become more specialized and interdisciplinary, currently requiring collaboration among specialists in nephrology, transplantation medicine, medical oncology, critical care, clinical pharmacology/pharmacy, and palliative care, in addition to surgeons and urologists. To identify key management

issues in nephrology relevant to patients with malignancy, KDIGO (Kidney Disease: Improving Global Outcomes) assembled a global panel of multidisciplinary clinical and scientific expertise to convene a controversies conference on onco-nephrology in Milan, Italy, in December 2018. This report addresses the renal-related issues in hematological malignancies and discusses the burden of cancer in kidney transplant recipients.

KIDNEY DISEASE IN HEMATOLOGY

Recognizing and preventing tumor lysis syndrome

TLS is a hemato-oncologic emergency resulting from spontaneous or chemotherapy-induced tumor cell death. It can be classified as a laboratory or clinical form in which metabolic disturbances can overwhelm homeostatic capacity and have severe clinical consequences. The development of new oncology drugs has outpaced investigations concerning TLS, and thus the incidence and prevalence of TLS are not well defined. TLS risk is influenced by tumor type, tumor burden, patient characteristics, and type of therapy. The commonly used definition of TLS[10] contains an outdated kidney injury component that should be updated to reflect the current KDIGO AKI definition.[11]

To evaluate risk of TLS, electrolytes (sodium, potassium, phosphorus, magnesium, and calcium), estimated glomerular filtration rate (eGFR), and uric acid should be measured in all patients at baseline. The frequency of laboratory measurements depends on the risk profile. The predictive role of baseline uric acid for TLS is currently unknown. With the expanded availability of several novel targeted molecular and immune cell–based agents, such as monoclonal antibodies, cyclin-dependent kinase inhibitors, proteasome inhibitors, pro-apoptotic agents, and chimeric antigen receptor (CAR)–T cells, the spectrum of neoplasms with a risk of TLS is expanding and now includes chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, and several solid tumors.[12,13]

Xanthine oxidase inhibitors (XOIs) are the drug class of choice for preventing TLS, although the dose and target level of uric acid has not been defined (Table 1[14–16]).[17] For established TLS patients with normal kidney function, allopurinol is the preferred XOI. Febuxostat is an alternative for lowering uric acid; in the FLORENCE trial, 1 fixed dose of febuxostat started 2 days prior to chemotherapy initiation and continued for only 7 to 9 days achieved a significantly superior serum uric acid control compared with allopurinol, with comparable kidney function preservation and safety profile. For longer treatments (as with gout), febuxostat's safety profile remains uncertain. Short febuxostat administration may be a good alternative, especially considering that a quick response of serum uric acid is achievable.[14,18] Although febuxostat is now generic and its cost has decreased, it is still more expensive than allopurinol, making cost a factor in many regions. Alternatively, rasburicase is a very effective treatment for TLS,[19] although its optimal dose and frequency are not known, and availability and cost can be prohibitive. Recent reports indicate that single-dose rasburicase is efficient in preventing and managing TLS,[20] which could broaden accessibility. Sequential therapy of rasburicase and an XOI has been shown to be effective.[21]

Evidence regarding the prevention of TLS is limited. In trials of acute leukemias, reported TLS rates were 42% and 53% with alvocidib (with sequential cytarabine and mitoxantrone) and 15% with dinaciclib. Venetoclax has the highest associated risk for inducing TLS in chronic lymphocytic leukemia (8.3% and 8.9% in 2 trials), whereas TLS incidence is $\leq$5% with brentuximab vedotin (for anaplastic large cell lymphoma), carfilzomib and lenalidomide (for multiple myeloma), dasatinib (for acute lymphoblastic leukemia), and oprozomib (for various hematologic malignancies).[22] Although the predictive role of baseline uric acid for TLS is still debated, the guidelines for pediatric and adult TLS suggest that the risk of developing TLS and renal events is increased by 1.75- and 2.21-fold, respectively, for every mg/dl increase in serum uric acid.[23]

Issues related to multiple myeloma

Extracorporeal treatment for managing multiple myeloma cast nephropathy. If extracorporeal treatments are used, levels of serum free light chains (FLCs) will need to be monitored. High levels of FLCs are associated with lower event-free and overall survival,[24] whereas rapid reduction of FLC leads to improved kidney and overall survival.[25] Supportive measures and chemotherapy should always be started as soon as possible, before therapeutic plasma exchange (TPE) or high cut-off hemodialysis (HCO-HD). It is unknown whether TPE improves kidney or overall outcome in multiple myeloma patients with high FLC (Table 1). Most trials investigating TPE in cast nephropathy are from the pre-bortezomib era, and it is unclear whether newer agents lead to a lower integral of FLC concentration over time. In a trial published in 1988 including 29 participants, TPE demonstrated efficiency in removing light chains from circulation and improving outcomes.[26] However, in a larger patient population undergoing chemotherapy prior to bortezomib introduction (n = 104), TPE failed to improve the composite endpoint of death, dialysis dependence, or glomerular filtration rate <30 ml/min per 1.73 m^2 at 6 months.[27] Anecdotal data with high-volume selective plasma exchange are encouraging.[28] Extracorporeal elimination of FLC is not indicated in patients with normal kidney function. Hyperviscosity syndrome is an indication for TPE, irrespective of other treatment goals.

The role of FLC levels for initiating or discontinuing extracorporeal treatments is unknown. HCO-HD can effectively remove light chains[29] and has been shown to remove cytotoxic agents[30] and analgesics.[31] Data from uncontrolled trials suggest that using HCO-HD can lead to improvement in renal endpoints.[32,33] However, in a study of patients with myeloma cast nephropathy treated with a bortezomib-based chemotherapy regimen, the use of HCO-HD compared with conventional hemodialysis did not result in a statistically

significant difference in hemodialysis independence at 3 months.[34] During a 2-year follow-up of 90 patients enrolled in the open-label, phase 2, randomized controlled EuLITE trial,[35] 98 and 82 serious adverse events were reported in the HCO-HD and high-flux hemodialysis (HF-HD) groups, respectively. The most common serious adverse events were infections, cardiovascular and thrombotic events, and events related to the musculoskeletal systems. During the first 90 days, 26 infections (including 14 lung) were reported in the HCO-HD group, and 13 infections (including 3 lung) were reported in the HF-HD group.[35] Together these results do not support initiation of HCO-HD phase 3 studies. Given the need to improve therapeutic strategies in myeloma cast nephropathy, combining efficient FLC removal techniques with effective but tolerable chemotherapy warrants further investigation.[15]

A 2012 report from animal models identified a competitive inhibitor cyclized peptide that interferes with the binding of the light chains with Tamm-Horsfall protein,[36] possibly paving the way for eliminating the need for extracorporeal elimination. However, human studies are yet to be conducted.

Managing multiple myeloma–related bone disease. Although bisphosphonates are contraindicated in patients with advanced kidney disease, single-dose (30 mg) pamidronate for hypercalcemia does not require dose adjustment if eGFR is >30 ml/min per 1.73 m^2. Twelve-month study data indicate pamidronate may also be used in hemodialysis patients.[37]

Choosing between bisphosphonate or denosumab therapy. For newly diagnosed multiple myeloma, denosumab is non-inferior to zoledronic acid in time to skeletal-related events and has a lower renal toxicity.[38] There are, however, limited data supporting non-inferiority of denosumab safety relative to alendronate in hemodialysis patients, especially regarding risk of severe hypocalcemia.[39] Anecdotal data suggest the same is true for peritoneal dialysis.[40] Whether bisphosphonate is associated with adverse risks needs to be examined (Table 1).

Managing calcineurin inhibitors

In recipients of allogeneic stem cell transplants, tacrolimus is associated with a lower likelihood of AKI relative to cyclosporine. Drug blood levels should be measured at regular intervals. It is unknown if lowering calcineurin inhibitor levels to reduce the risk of AKI elevates the risk of graft-versus-host disease. However, cyclosporine levels >195 μg/l on post-transplant day 10 have been associated with significantly reduced likelihood of acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation.[41] It is unclear whether there is any role for kidney biopsy in patients with AKI who take calcineurin inhibitors.

Because calcineurin inhibitors can cause transplant-associated thrombotic microangiopathy, cases of hypertension, thrombocytopenia, and elevated lactate dehydrogenase should prompt suspicion of thrombotic microangiopathy.

The role of kidney biopsy for kidney recovery therapy in cast nephropathy

Kidney biopsy is strongly recommended to confirm cast nephropathy in AKI after chemotherapy initiation. Therapy should not be delayed while waiting for biopsy results. Any concern that there is an increased bleeding risk in this patient population is not supported by the literature.[42]

The proportion of noncast nephropathy in patients with suspected cast nephropathy is unknown. Investigating whether there are biomarkers that can be used to predict the probability of developing cast nephropathy may be worthwhile. The 2014 International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma defined light chain cast nephropathy as a myeloma defining event and identified validated biomarkers of malignancy.[43]

Determining which patients with monoclonal gammopathy of renal significance should be offered treatment

All patients with monoclonal gammopathy of renal significance (MGRS) and a target for chemotherapy (e.g., Ig light chain amyloidosis, light chain deposition disease, C3 glomerulopathy, post-transplantation lymphoproliferative syndromes, immunotactoid, etc.) should be offered treatment. In a consensus report from the International Kidney and Monoclonal Gammopathy (IKMG) Research Group,[44] MGRS was redefined as a clonal proliferative disorder that produces a nephrotoxic monoclonal Ig and does not meet previously defined hematological criteria for treatment of a specific malignancy. The diagnosis of MGRS-related disease is established by kidney biopsy and immunofluorescence studies to identify the monotypic Ig deposits (although these deposits are minimal in patients with either C3 glomerulopathy or thrombotic microangiopathy). Accordingly, the IKMG recommends performing a kidney biopsy in suspected cases of MGRS; serum and urine protein electrophoresis and immunofixation, as well as analyses of serum FLCs, should also be performed to identify the responsible monoclonal Ig. Finally, bone marrow aspiration and biopsy should be conducted to identify the lymphoproliferative clone. Flow cytometry can be helpful in identifying small clones. Additional genetic tests and fluorescent *in situ* hybridization studies are helpful for clonal identification and for generating treatment recommendations. However, pitfalls do exist at each diagnostic step, and a high degree of clinical suspicion is still required when diagnosing MGRS.[45] Indications and timing for starting treatment remain controversial (Table 1), although any decisions should be shared among hematologists, nephrologists, and patients in a multidisciplinary fashion.

Chemotherapy for treating monoclonal gammopathy of renal significance

Treatment for MGRS generally includes a proteasome inhibitor, although the optimal combination of agents is unknown.[46] Parameters to judge the renal effect of therapy are change in eGFR and degree of proteinuria.

Candidacy for kidney transplantation in patients with myeloma and amyloidosis on dialysis

Anecdotal reports[47] suggest that kidney transplantation can be considered after complete remission of myeloma[48] and can be pursued after complete hematological remission of amyloidosis. However, the optimal duration of remission prior to transplantation is not known (Table 1). The absence of extrarenal organ dysfunction due to amyloid is considered to be a prerequisite for transplantation. N-terminal–pro-B-type natriuretic peptide as a marker of heart failure is of limited use in advanced CKD.

Dosing of cytotoxic agents in patients with CKD G3b–G5D

Dosing studies in patients with CKD G3b–G5D are not part of the process for regulatory approval of therapeutics in either the United States or Europe. Therefore, data for determining optimal dosing of most cytotoxic agents in patients with CKD G3b–G5D are lacking.[49] Regulatory agencies need to address this issue, and one strategy could be to make postmarketing studies mandatory (Table 1).

Role of new sorbent devices in hematology/oncology patients

There is no proven benefit of using new sorbent devices in hematology/oncology patients.[50] It is unknown whether adsorbent devices offer a benefit over anti–interleukin-6 therapy approaches or if there is any indication for using the new adsorbing devices in the setting of AKI stage 3 with need for kidney replacement therapy.

Analgesics for long-term pain management in CKD patients with cancer-related pain

Appropriate treatment of pain in cancer patients remains an unresolved issue. Unsubstantiated avoidance of opioids is not justified in patients with malignancies. Nonsteroidal anti-inflammatory drugs must be used with caution in patients with advanced CKD or at high risk for it. The benefit-to-risk ratio of gabapentin and pregabalin should be assessed on an individual basis. All components of World Health Organization guidelines should be considered.[51]

Determining which hematological cancer patients with CKD can be treated with erythropoietin-stimulating agents

In hematological cancer patients, iron status should be optimized before starting erythropoietin-stimulating agent (ESA) treatment. Data regarding the potential adverse effects of ESAs in patients with solid tumors cannot be applied to hematological patients. Risks of a tumor-promoting activity of erythropoietin should be weighed against benefits. Similarly, target hemoglobin levels are unclear. Newer oral ESAs have not been evaluated in this patient population.

Decision-making for initiating or terminating kidney replacement therapy

Expectations of what dialysis can reasonably accomplish in hematological cancer patients are often unrealistically high among patients and their caregivers[52]; an estimate of overall prognosis based on each patient's comprehensive status (including age, performance status, frailty, malnutrition, comorbidities, and co-medications) is thus mandatory. An interdisciplinary team approach and improved communication between hematologists/oncologists and nephrologists is necessary for facilitating the discussion on whether to initiate kidney replacement therapy. Empathic communication of information with patients using a shared decision-making approach can then lead to an informed decision that respects patient autonomy and is consistent with the patient's goals and personal values.[53]

Predictors of short-term survival after starting kidney replacement therapy are not available for hematological cancer patients. Not starting kidney replacement therapy is a valid approach, because outcomes may be similar to dialysis therapy with better quality of life. In general, advanced directives are underutilized, and it is possible that counseling on advanced directives could be an effective strategy to avoid decision-making under emergency circumstances.

For patients not starting dialysis or discontinuing dialysis, palliative care should be considered and offered. Another possible approach is undergoing a trial period of kidney replacement therapy in the intensive care unit.

CANCER IN KIDNEY TRANSPLANT RECIPIENTS

Epidemiology

Robust and convincing registry data indicate that the overall risk of cancer in kidney transplant recipients is increased by at least 2- to 2.5-fold compared with the general population matched for age and gender (Table 2[1,2,54–64]).[1,54–56] Patients who have the greatest increased risk are those with a virally related cancer such as Kaposi sarcoma (20-fold), cervical cancer (5- to 10-fold), and post-transplant lymphoproliferative disease.[1,54] Other solid organ malignancies such as colorectal and lung cancers (approximately 2- to 3-fold) incur a modest increase in incidence compared with age- and gender-matched general populations.[1,54] Other cancers, such as breast and prostate, do not incur an excess risk among transplant recipients. Because the increased risk of cancer has also been demonstrated in patients on dialysis and those with early- to moderate-severity CKD, the increased cancer burden in CKD settings is likely not related to immunosuppression alone but may also be driven by conditions associated with CKD, such as uremia and chronic inflammation.[57,59,62]

Cancer is a leading cause of death among transplant recipients.[2] Data suggest the risk of death in the transplant population is increased by at least 2- to 3-fold compared with the general population matched for age and gender.[63] The causes of increased risk are unclear but may result from increased cancer incidence, differences in tumor biology in the context of immunosuppression, and/or differences in chemotherapeutic approach, particularly among recipients with coexisting comorbidities. The increased risk of cancer and cancer-related deaths observed in transplant populations is attributed predominantly to viral-related cancers, such as post-transplant lymphoproliferative disease (Epstein-Barr virus), Kaposi sarcoma, primary effusion lymphoma (human

Table 2 | Standardized incidence ratio of site-specific cancers in North America, Europe, Asia, and Australasia

	Asia						
	Hong Kong[2,59]		Korea	Taiwan[60,61]		Australia[54,55,57]	
Site	Dialysis	KT	KT	Dialysis	KT	Dialysis	KT
All sites	1.44 (1.26–1.65)	2.94 (2.6–1.6)	3.54 (2.9–4.3)	1.4 (1.3–1.4)	4.12	1.36	3.27
Bladder	2.5 (1.1–4.7)	8.22 (4.7–14.5)	4.06 (0.46–14.7)	8.2 (6.7–9.9)	47.8	NA	NA
Brain	NA	NA	12.9 (2.6–37.7)	NA	NA	1.1 (0.59–2.05)	0.57 (0.16–1.46)
Breast	1.65 (1.0–2.7)	1.66 (1.2–2.7)	2.7 (0.9–5.9)	1.2 (1.0–1.5)	1.55	1.25 (0.99–1.55)	1.03 (0.78–1.34)
Cervical	4.1 (1.6–8.5)	7.19 (3.8–13.4)	6.05 (1.2–17.6)	0.9 (0.7–1.1)	0.81	2.58 (1.38–4.42)	2.49 (1.33–4.27)
Colorectal	1.53 (1.1–2.1)	1.75 (1.2–2.5)	0.48 (0.1–2.7)	1.0 (0.9–1.1)	0.96	1.18 (0.9–1.5)	2.36 (1.9–2.9)
Esophagus	NA	1.12 (0.3–1.2)	NA	NA	1.96	1.7 (0.96–2.7)	3.82 (2.3–6.0)
Kaposi sarcoma	NA	NA	446.0 (89.7–1305)	NA	NA	57.8 (21.2–125.9)	207.9 (113–348)
Kidney	NA	12.5 (8.5–18.4)	16.31 (7.4–30.9)	7.2 (5.7–8.9)	79.0	NA	NA
Larynx	NA	NA	NA	NA	2.98	1.02 (0.41–2.11)	2.1 (0.96–3.98)
Leukemia	NA	2.15 (0.9–6.2)	27.8 (7.3–69.3)	0.4 (0.2–0.7)	2.14	1.14 (0.74–1.77)	2.46 (1.65–3.67)
Lip	NA	NA	NA	NA	1.96	3.68 (2.46–5.28)	47.1 (41.7–52.9)
Liver	1.2 (0.7–2.0)	2.53 (1.6–3.9)	2.74 (1.0–5.9)	1.4 (1.2–1.5)	3.57	2.25 (1.23–3.77)	3.2 (1.5–5.9)
Lung	0.94 (0.6–1.3)	1.68 (1.2–2.4)	1.79 (0.6–3.9)	0.5 (0.5–0.6)	1.5	1.59 (1.33–1.88)	2.45 (2.0–2.97)
Melanoma	NA	9.09 (2.3–36.3)	NA	NA	NA	1.06 (0.81–1.38)	2.53 (2.08–3.05)
Myeloma multiplex	1.31 (0.15–4.7)	NA	24.02 (6.4–61.5)	NA	NA		
NHL	1.69 (0.7–3.5)	15.79 (11.9–20.9)	28.6 (7.7–73.2)	1.3 (0.9–1.7)	8.26	1.36 (0.94–1.9)	9.86 (8.37–11.5)
NMSC	1.75 (0.75–3.4)	7.38 (4.9–11.2)	7.58 (2.0–4.1)	NA	1.41	NA	NA
Ovary	NA	7.3 (4.6–11.5)	3.4 (0.1–18.9)	NA	NA	1.0 (0.43–1.98)	1.15 (0.46–2.38)
Pancreas	1.17 (0.3–2.9)	1.57 (0.5–4.9)	2.73 (0.3–10.0)	NA	3.71	1.17 (0.69–1.8)	1.21 (0.56–2.3)
Prostate	0.6 (0.1–0.8)	0.88 (0.4–1.9)	2.45 (0.5–7.2)	0.5 (0.4–0.7)	1.11	0.66 (0.52–0.83)	0.95 (0.68–1.29)
Soft tissue	NA	NA	NA	NA	NA	1.26 (0.41–2.93)	4.3 (2.13–7.21)
Stomach	1.1 (0.5–2.2)	2.85 (1.6–5.0)	NA	0.9 (0.7–1.1)	1.86	1.5 (1.0–2.19)	1.8 (1.1–2.9)
Thyroid	3.4 (1.3–7.5)	4.35 (2.4–7.6)	NA	2.2 (1.5–3.1)	5.59	9.23 (6.53–12.67)	6.9 (4.69–9.79)
Uterus	1.7 (0.4–4.2)	1.44 (0.5–4.5)	NA	NA		1.07 (0.53–1.91)	1.74 (0.92v2.97)

KT, kidney transplant; NA, not available; NHL, non-Hodgkin lymphoma; NMSC, nonmelanoma skin cancer.
Data are presented as standard incidence ratio (95% confidence interval).

herpesvirus 8), skin, oropharynx, tonsil, anogenital cancers (cervix, vagina, vulva, anus, penis [human papillomavirus]), Merkel cell carcinoma (Merkel cell polyomavirus), and hepatocellular carcinoma (hepatitis B and C virus).[61,64]

Epidemiologic data on the incidence and outcomes of transplant recipients with cancer are based on observational registry analyses. Reporting to these registries is predominantly voluntary, and questions regarding their completeness have been raised.[60] Specific concerns relate to how outcomes were ascertained; whether data are accurately and fully reported; the lack of details pertaining to histology, stage, and longer-term outcomes; the lack of a robust reference standard—for instance, data linkage to cancer registries where data collection is mandatory; and the lack of a universal coding system defining cancer outcomes. Most transplant recipient registries are developed in high-income countries. It is crucial to support the development of robust and transparent dialysis and transplant registries in low- to middle-income countries. Research opportunities and priorities are listed in Table 3.

Donor cancer transmission in transplant recipients

Cancer transmission from donors is rare. The estimated disease transmission rate (from both living and deceased donors) varies between 1 and 2 cases per 10,000 organ transplant recipients, although these estimates are subject to reporting bias[58] and may underrepresent the actual disease incidence. The risk of disease transmission is dependent on the type of cancer, ranging from less than 0.1% among non-invasive *in situ* cancers to more than 10% among malignant cancers such as melanomas.[2] Although disease transmission is infrequent, it can be a devastating event for patients, their families, and transplanting teams, because the prognoses of recipients with donor-transmitted disease are generally poor.[65] Deaths associated with donor-transmitted disease are frequently reported in the media, which raises concerns and fears within the community.

The median time from transplantation to cancer diagnosis is approximately 8 months (interquartile range 3–13 months) but varies with cancer type.[58] Among recipients with donor-transmitted cancers, the risk of death is greatest among those with transmitted lung cancers and melanomas, with fewer than 50% surviving 2 years after diagnosis. Effective and efficient preventive and screening strategies are therefore needed to minimize any disease transmission risk. It is mandatory that all deceased and living potential donors are screened for transmissible disease including infections and malignancies. The Organ Procurement and Transplantation Network/United Network for Organ Sharing, the British Transplantation Society, European Directorate for the Quality of Medicines and Health Care, and the Transplantation Society of Australia and New Zealand have all developed policy

Table 2 | (Continued) **Standardized incidence ratio of site-specific cancers in North America, Europe, Asia, and Australasia**

Europe[57]				North America				
Denmark[62]		Germany[63,64]	Sweden[62]	Canada[1]	United States[56,57]		World (aggregated data)[58]	
Dialysis	KT	KT	KT	KT	Dialysis	KT	Dialysis	KT
1.6 (1.5–1.6)	2.9 (2.8–3.1)	4.3 (4.0–4.7)	3.5 (3.4–3.7)	2.5 (2.3–2.7)	1.2 (1.2–1.2)	2.1 (2.06–2.14)	NA	NA
1.8 (1.5–2.1)	2.1 (1.6–2.8)	2.8 (1.8–4.2)	2.0 (1.6–2.6)	2.0 (1.3–3.0)	1.4 (1.3–1.5)	NA	2.51 (1.85–3.41)	3.15 (1.27–7.8)
1.1 (0.8–1.5)	1.1 (0.7–1.7)	3.99 (2.0–7.3)	1.2 (0.9–1.7)	1.3 (0.5–2.5)	NA	0.76 (0.55–1.01)		1.0 (0.64–1.57)
1.3 (1.0–1.5)	1.3 (1.1–1.7)	1.46 (1.0–2.0)	1.1 (0.9–1.4)	1.3 (1.0–1.7)	0.8 (0.8–0.9)	0.85 (0.77–0.93)	1.15 (0.9–1.46)	1.13 (0.99–1.29)
2.0 (1.2–3.5)	2.6 (1.6–4.5)	4.42 (2.9–6.4)	2.5 (1.5–4.1)	1.6 (1.3–1.6)	2.5 (2.2–2.8)	1.03 (0.75–1.38)	1.76 (1.09–2.86)	2.2 (1.56–3.1)
1.5 (1.2–1.7)	2.4 (1.9–3.1)	1.28 (0.9–1.8)	2.4 (2.0–2.9)	1.4 (1.0–1.8)	1.27 (1.23–1.3)	1.24 (1.15–1.34)	1.16 (0.9–1.43)	1.06 (0.66–1.72)
1.9 (1.3–2.7)	1.9 (1.0–3.4)	NA	1.2 (0.6–2.3)	1.5 (0.5–3.6)	NA	1.56 (1.26–1.91)	NA	NA
NA	NA	142.3 (71–259)	NA	NA	NA	61.4 (50.95–73.49)	NA	59.48 (24.43–144.86)
2.8 (2.2–3.7)	5.9 (4.4–7.8)	17.6 (14.0–21.8)	5.8 (4.8–7.0)	7.3 (5.7–9.2)	3.7 (3.5–3.9)	4.65 (4.32–4.99)	4.87 (4.14–5.72)	9.7 (5.69–16.53)
1.7 (1.0–2.7)	1.9 (0.9–3.7)	NA	3.0 (1.7–5.3)	1.7 (0.7–3.4)	NA	1.59 (1.29–1.95)	NA	1.53 (0.84–2.79)
1.2 (0.8–1.7)	1.3 (0.7–2.4)	2.19 (0.76–5.12)	1.6 (1.1–2.4)	2.3 (1.3–3.6)	1.9 (1.7–2.0)	3.47 (2.46–4.77)	1.02 (0.55–1.9)	1.62 (1.23–2.14)
3.9 (2.0–7.5)	12.7 (7.1–23)	NA	NA	31.4 (23.5–40.8)	NA	NA	NA	29.74 (16.96–52.17)
2.0 (1.4–3.0)	3.4 (2.0–5.9)	3.96 (1.9–7.2)	4.0 (2.8–5.6)	1.8 (0.6–4.3)	1.5 (1.3–1.7)	11.56 (10.83–12.33)	1.39 (1.28–1.51)	2.52 (1.71–3.73)
1.5 (1.4–1.7)	2.6 (2.2–3.1)	2.67 (1.9–3.7)	2.3 (1.9–2.7)	2.1 (1.7–2.5)	1.1 (1.1–1.2)	1.97 (1.86–2.08)	0.98 (0.77–1.24)	1.52 (1.15–1.99)
1.4 (1.1–1.9)	1.8 (1.3–2.6)	4.13 (2.76–5.9)	2.4 (1.9–3.0)	1.9 (–1.2 to 3.0)	NA	2.38 (2.14–2.63)	2.83 (1.28–6.23)	2.05 (1.52–2.78)
2.5 (1.7–3.6)	2.2 (1.1–4.5)	7.33 (3.7–13.4)	2.3 (1.5–3.6)	3.9 (2.1–6.6)		5.2 (5.0–5.3)	4.15 (3.1–5.56)	2.96 (1.94–4.52)
1.6 (1.2–2.2)	5.1 (4–6.6)	NA	7.9 (6.8–9.2)	8.8 (7.4–10.5)	1.7 (1.5–1.8)	7.54 (7.17–7.93)	1.16 (0.86–1.55)	6.05 (4.11–8.9)
5.3 (4.7–5.9)	41.5 (37.8–45.5)	52.7 (44.7–61.7)	44.7 (42.0–47.5)	NA	NA	13.85 (11.92–16.0)	NA	15.18 (8.08–28.52)
0.8 (0.4–1.4)	1.2 (0.6–2.3)	NA	1.6 (1.0–2.5)	1.5 (0.6–3.0)	NA	0.95 (0.72–1.24)	NA	1.39 (0.69–2.77)
1.8 (1.3–2.3)	1.2 (0.6–2.1)	NA	2.2 (1.5–3.0)	1.1 (0.4–2.2)	1.08 (1.01–1.15)	1.46 (1.24–1.71)	NA	1.55 (1.19–2.0)
0.9 (0.8–1.0)	1.0 (0.7–1.4)	2.04 (1.5–2.7)	0.9 (0.8–1.1)	0.9 (0.6–1.3)	0.7 (0.6–0.7)	0.92 (0.87–0.98)	0.87 (0.69–1.09)	1.14 (0.94–1.37)
1.7 (0.9–3.1)	4.8 (2.7–8.4)	NA	2.2 (1.1–4.1)	4.8 (2.3–8.8)	NA	2.25 (1.74–2.87)	NA	NA
1.5 (1.1–2.2)	2.5 (1.6–4.1)	1.36 (0.7–2.3)	2.1 (1.5–2.9)	2.1 (1.2–3.4)	1.3 (1.2–1.4)	1.67 (1.42–1.96)	1.03 (0.71–1.5)	1.92 (1.6–2.31)
3.0 (1.7–5.5)	4.2 (2.2–7.7)	5.09 (2.8–8.7)	4.9 (3.3–7.3)	5.0 (3.1–7.4)	2.4 (2.1–2.8)	2.95 (2.58–3.34)	4.92 (1.43–14.9)	3.75 (2.5–5.62)
1.2 (0.8–1.8)	1.4 (0.8–2.5)	NA	1.0 (0.6–1.6)	0.9 (0.3–2.0)	0.9 (0.8–1.0)	NA	0.96 (0.78–1.19)	1.37 (0.75–2.51)

requirements for evaluating organs from live and deceased donors. Despite these recommendations, variations in practice exist. Given the increasing number of patients on the active kidney transplant waitlist and an annual death rate on the overall waitlist of approximately 5%, it is imperative to maximize the utilization of available donor organs. Patients should be well-informed about the projected risk of disease transmission with higher-risk donors relative to the risk of premature death on dialysis. A structured, personalized, shared decision-making approach should be developed and implemented to improve the value of care to potential transplant recipients.

Transplantation in patients with a prior cancer history

Recommendations for transplantation eligibility in patients with a prior cancer specify that potential candidates should be in complete remission after radical oncological therapy, with no evidence of active disease. However, recommended waiting times prior to listing vary considerably between guidelines.[66] There is limited quality evidence to guide decision-making. The waiting time from complete remission to listing should depend on the risks of disease recurrence and survival thereafter. Recent systematic reviews of observational studies have shown that excess risk of cancer-specific death among recipients with a prior cancer history is at least 3-fold higher than those without a prior cancer history.[67] Emerging data suggest waiting time is not a key determinant for disease recurrence after transplantation[68]; however, such data should be interpreted with caution as they are subject to potential selection bias and era effects.

Given changing patient characteristics and the advent of new therapies such as targeted therapies, checkpoint inhibitors, or a combination of the 2 for oncological management, the criteria for listing should not be fixed, as had been done historically (Figure 1).[69] Rather, criteria should be dynamic and personalized and should take into consideration patient preferences and the potential trade-offs between the quality of life and survival gains with transplantation, the probability of premature death while undergoing dialysis, and the risk of disease recurrence and cancer-related death after transplantation (Figure 2).

Cancer screening in kidney transplant recipients

Transplant screening provides an opportunity to detect and treat premalignant lesions. The current screening guidelines in the transplant population are largely extrapolated and adopted from the general population, and there is no trial-based evidence to support them.[70,71] The harms, test performance, and benefits incurred through screening in the transplant population are likely to be different from those of the general population. A recent study of screening colorectal cancer using one-time fecal immunochemical diagnostic tests in patients with CKD (including kidney transplant recipients) has shown favorable performance, but major complications from

Table 3 | Research priorities in malignancy and kidney transplantation

	Research priorities
Epidemiology	• Generate longitudinal data to investigate the outcomes of cancer survivors after transplantation and cohorts to study risk that may be adapted to answer specific questions on outcomes • Unify cancer-specific coding (ICD-O) • Harmonize and merge data sources from country-specific transplantation registries • Capture granular data on histology, stage, and outcomes • Develop a quality and global nephrology registry (CKD, dialysis, and transplant)
Donor-derived cancers	• Initiate a registry for global donor surveillance and vigilance • Develop a transplant outcomes registry • Create a prediction and simulation model using large datasets that allow assessment of the following: ○ Risk of transmission of a specific donor ○ Risk of death/survival after cancer transmission ○ Risk of death on dialysis vs. risk of death after malignancy in KT • Create a patient/doctor shared-decision model • Harmonize data from global registries and data repositories • Develop and validate models that predict the risk of disease transmission using population-based, age-specific cancer risk data in the general population and known cancer-specific mortality data in the transplanted population. Aggregated registry data will provide opportunities to constantly update the modelling and allows continual refinement of the evidence. • Develop an electronic patient reported outcomes (e-PROs) platform to obtain patient-reported outcome measures • Create a decision-analytic model that takes into consideration patient preferences, PROs, and comparative survival data (with and without transplantation) to guide decision-making • Create a clinical-decision support derived from aggregated data across global registries to provide guidance on tailoring care for individual candidates • Develop a well-designed, international policy framework that will safeguard recipients against disease transmission
Recipients with cancer history	• Generate comprehensive and complete follow-up records of observational data on cancer recurrence and cancer-related outcomes after transplantation • Develop fluid biopsy for early cancer detection • Develop methods for immune profiling and genomic profiling
Cancer screening in KT	• Create a global survey for characterizing cancer screening across major nephrology and transplantation centers • Conduct RCT for PTLD screening using EBV DNA • Conduct an intervention trial for renal cell carcinoma screening in the at-risk population
KT education in cancer protection	• Conduct an observational study (exposure, interventions, outcomes) focused on skin cancer • Establish a tailored, individualized educational program • Provide educational websites, skin cancer prevention, and health promotion/e-health
Cancer management after KT	• Create a rare cancer registry • Create a rare cancer protocol • Partner with pharmaceutical companies to develop novel interventions for the management of cancer after kidney transplantation • Conduct RCT with the new cancer therapies in KT patients, including those with low GFR levels • Conduct RCT to assess mTORs vs. other immunosuppressants in cancer and KT patients

CKD, chronic kidney disease; EBV, Epstein-Barr virus; GFR, glomerular filtration rate; ICD-O, International Classification of Diseases for Oncology; KT, kidney transplantation; mTORs, mammalian targets of rapamycin; PRO, patient-reported outcomes; PTLD, post-transplant lymphoproliferative disease; RCT, randomized controlled trial.

workup colonoscopies are high.[72] There are also considerable variations in screening practices across major transplant centers worldwide. Population-based screening programs for cervical, colorectal, breast, and prostate cancers are universal in most high-income countries. Given the increased risk of other cancer types, such as kidney cancer, post-transplant lymphoproliferative disease, and lung and skin cancer, routine screening for these cancers is implemented in many centers worldwide. However, the evidence to support the frequency, modality, and target population for screening is uncertain.

Despite the current screening recommendations, uptake for routine breast and cervical screening in the transplanted population remains low.[73] Reasons for the low uptake are multifactorial. Qualitative work has indicated that patients are cognizant of their susceptibility to the higher risk of cancer but also prioritize other issues associated with their kidney disease and allografts.[74] They are also concerned about the potential harms and costs associated with routine testing.[75,76] Quality evidence is needed regarding routine screening of other cancer types. Several suggestions for broadening the evidence base are listed in Table 3.

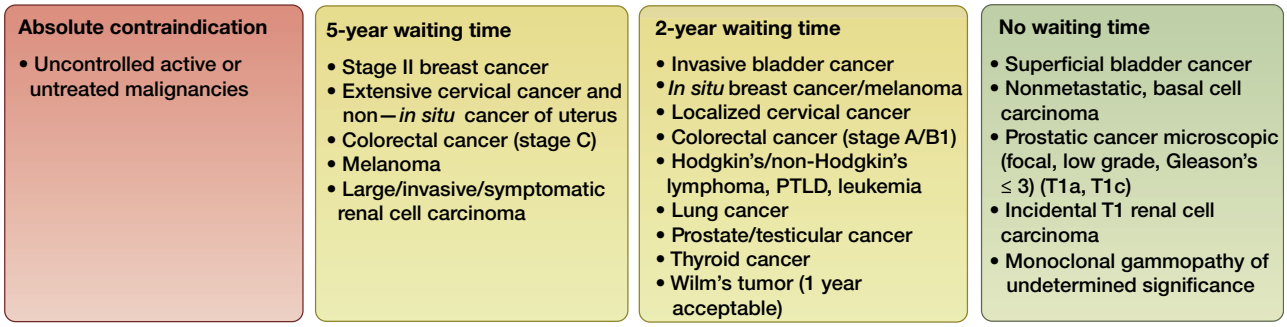

Figure 1 | Historic fixed waiting time recommendations for transplantation. PTLD, post-transplant lymphoproliferative disease. Adapted from Sprangers B, Nair V, Launay-Vacher V, et al. Risk factors associated with post-kidney transplant malignancies: an article from the Cancer-Kidney International Network. *Clin Kidney J.* 2018;11:315–329.[69] © The Author 2017. Published by Oxford University Press on behalf of ERA-EDTA.

Patient education

Education strategies for preventing cancer among transplant recipients exist for skin cancers but not for other solid organ cancer types. Patient education should begin early, meaning before or during the identification of progressive CKD. An educational program should also respect patient perspectives and preferences. E-health websites could serve to provide thorough education at a basic reading level.

Management of cancer after kidney transplantation

The management of cancer after kidney transplantation is complex. For patients who develop cancer after kidney transplantation, the approach has traditionally focused on reducing overall immunosuppression, with administration of chemotherapy agents managed by a medical oncologist. Dose reduction of immunosuppression after transplantation is likely to depend upon cancer type, stage, and many other factors. However, this approach needs to be balanced carefully with the risk of allograft rejection. Prospective trial-based data to inform immunosuppression management, including dose reduction and/or immunosuppression cessation, are lacking. Mammalian target of rapamycin inhibitors (sirolimus and everolimus) may have a promising role in managing cancer after transplantation (particularly with nonmelanocytic skin cancers and Kaposi sarcomas), owing to their simultaneous immunosuppressive and anticancer effects.[77–79]

New targeted anti-cancer therapies including checkpoint inhibitors and other immunotherapies are now available to treat advanced-stage solid organ and hematological malignancies. Across multiple tumor types these agents have greater efficacy than standard cytotoxic therapies. However, the majority of intervention trials assessing the effectiveness of new agents have excluded transplant recipients. The safety and efficacy profiles of these agents in immunosuppressed populations are unknown. In particular, there are case reports and series suggesting the use of anti-PD1, cytotoxic T-lymphocyte–associated antigen 4, and other immune modulators in transplant recipients can lead to acute allograft rejection.[80–83] This remains a controversial issue, because there are other case reports in which use of everolimus in lieu of calcineurin inhibitors did not prevent allograft rejection in patients receiving ipilimumab or pembrolizumab.[84,85] Development of a global collaborative cancer registry could allow data sharing and opportunities for industry

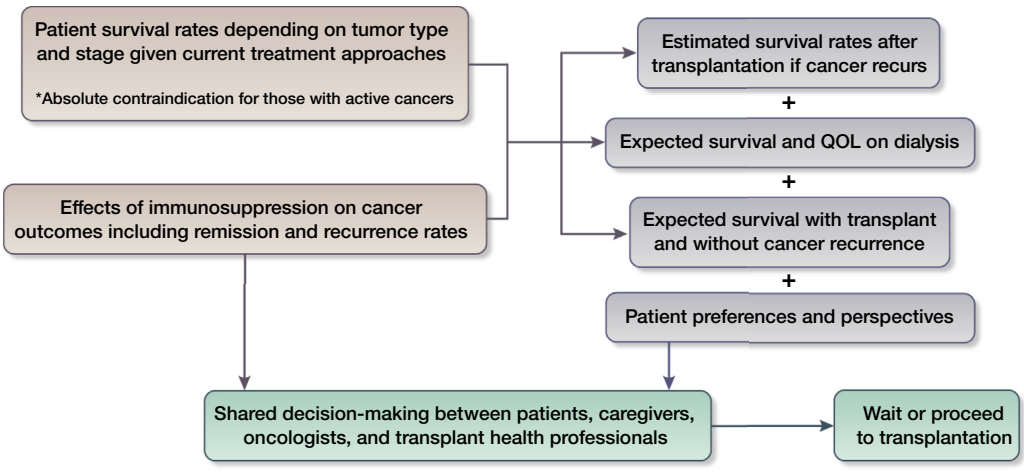

Figure 2 | Decision factors for transplantation in candidates with prior cancers in complete remission. QOL, quality of life.

partnerships and patient involvement in clinical trials of novel anti-cancer therapies.

CONCLUSION

The conference participants emphasized the importance of collaboration among nephrology, hematology/oncology, and transplant specialists, as well as pharmacists, in clinical care and clinical trials.

Despite its frequency, AKI is one component of TLS for which optimal prophylaxis and treatment and differential use of XOIs and rasburicase is not known. Lack of dosing and toxicity data for old and new drugs used for hematological and oncological diseases has resulted in acute and chronic renal injury. Pharmaceutical companies should invest in appropriate postmarketing studies to improve our ability to reduce adverse renal effects without compromising treatment efficacy. Multiple myeloma is one of the main hematological diseases leading to chronic dialysis dependence. Extracorporeal and pharmacological approaches must be optimized to reduce kidney damage and need for dialysis.

Although cancer transmission from kidney donors is rare, it is mandatory that all deceased and living potential donors be screened for malignancies. In potential transplant candidates with a history of cancer, waiting periods after cancer remission are recommended. Post-transplantation cancer screening should be tailored to the individual patient. The screening for kidney cancer, post-transplant lymphoproliferative disease, and lung and skin cancer should be implemented in transplant centers worldwide. In kidney transplant recipients diagnosed with cancer, treatment is less effective than in the general population. Current clinical practice relies on evidence from observational studies and registry analyses, but the process of collecting data and its quality requires improvement. Further research into the mechanisms of cancer pathogenesis, the utility of cancer screening, and the effects of different immunosuppression regimens is needed.

APPENDIX

Other conference participants

Ali K. Abu-Alfa, Lebanon; Hatem Amer, USA; Gernot Beutel, Germany; Jeremy R. Chapman, Australia; Xiaohong Chen, China; Jerzy Chudek, Poland; Laura Cosmai, Italy; Romano Danesi, Italy; Filippo De Stefano, Italy; Kunitoshi Iseki, Japan; Edgar A. Jaimes, USA; Kenar D. Jhaveri, USA; Artur Jurczyszyn, Poland; Rümeyza Turan Kazancioğlu, Turkey; Abhijat Kitchlu, Canada; Christian Kollmannsberger, Canada; Amit Lahoti, USA; Yang Li, China; Manuel Macía, Spain; Takeshi Matsubara, Japan; Dionysios Mitropoulos, Greece; Eisei Noiri, Japan; Mark A. Perazella, USA; Pierre Ronco, France; Mitchell H. Rosner, USA; Maria Jose Soler Romeo, Spain; Ben Sprangers, Belgium; Walter M. Stadler, USA; Paul E. Stevens, United Kingdom; Vladimír Tesař, Czech Republic; Verônica Torres da Costa e Silva, Brazil; David H. Vesole, USA; Anitha Vijayan, USA; Ondřej Viklický, Czech Republic; Biruh T. Workeneh, USA; Motoko Yanagita, Japan; Elena Zakharova, Russian Federation.

DISCLOSURE

JM declared having consultancy fees from Fresenius Medical Care and Vifor Pharma. AB declared having received consultancy fees from BMS, Merck Sharp & Dohme (MSD), Pfizer, and Roche; speaker honoraria from Bristol Myers Squibb (BMS) and MSD; and research support from BMS and Pfizer. FRD declared having received research support from National Institutes of Health. MG declared having received speaker honoraria from General Electric. MAG declared having received consultancy fees from Abbvie, Alnylam, Amgen, Annexon, Appellis, Celgene, Janssen, Medscape, Physicians' Education Resource, Prothena, Research to Practice, Sanofi, and Spectrum; stock options from Aurora Bio; speaker honoraria from Akcea, Johnson and Johnson, and Teva; and research support from National Institutes of Health and Spectrum. JTK declared having received consultancy fees from Amgen and Vifor Pharma; stock from Chemocentryx; speaker honoraria from ExThera Medical and Vifor Pharma; and grants from ExThera Medical; and JTK was an expert witness in vaccine injury cases trialed at the US Federal Court of Claims. PT declared having received consultancy fees from AstraZeneca, Eli Lilly, Novartis, Pfizer, Pierre Fabre, and Roche; and speaker honoraria from AstraZeneca, Eli Lilly, Novartis, Pfizer, Pierre Fabre, and Roche. GW declared having received research support from the National Health and Medical Research Council. DCW declared having received consultancy fees from Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Mundipharma, Napp, and Vifor Fresenius Medical Care Renal Pharma; and speaker's honoraria from Amgen, Astellas, AstraZeneca, Mundipharma, Napp, Pharmacosmos, and Vifor Fresenius Medical Care Renal Pharma. WCW declared having consultancy fees from Akebia, Amgen, AstraZeneca, Bayer, Daiichi Sankyo, Relypsa, and Vifor Fresenius Medical Care Renal Pharma. CP declared having consultancy fees from AstraZeneca, BMS, Eisai, EUSA, Ipsen, Merck Serono, MSD, Novartis, and Pfizer; stock from DNA; and research support from AstraZeneca, BMS, Eisai, EUSA, GE, Ipsen, Merck Serono, MSD, Novartis, and Pfizer; and CP was an expert witness for DNA. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

The conference was sponsored by KDIGO and supported in part by unrestricted educational grants from Amgen, Akebia Therapeutics, Boehringer Ingelheim, Fresenius Medical Care, GE Healthcare, and MediBeacon. We thank Jennifer King, PhD, for assistance with manuscript preparation. The conference agenda, discussion questions, and plenary session presentations are available on the KDIGO website: https://kdigo.org/conferences/onco-nephrology-conference/.

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