KDIGO Controversies Conference on Onco-Nephrology
Public Review Comments

As of Nov 13, 2018; Industry comments are highlighted in blue

David Vesole (John Theurer Cancer Center at Hackensack UMC)

This conference provides a venue for the interaction of oncology WITH nephrology in discussion of new therapies and the potential off target renal toxicity. I can offer expertise in the management of hematologic malignancies and stem cell transplant.

Rukshana Shroff (Great Ormond Street Hospital, London, UK)

This is a detailed and very comprehensive list of onco-nephrological issues. However, kidney tumours in children are not included. While several of the breakout group topics would involve childhood malignancies too, I realise that it may not be possible to include paediatric diagnostic / management plans in the discussions. Perhaps KDIGO will consider a separate work-stream or a separate conference to cover paediatric onco-nephrology? Thank you.

Shigeo Horie (Juntendo University Graduate School of Medicine)

Japanese Society of Nephrology, working with Japanese Society of Medical Oncology and Japanese Society of Clinical Oncology, has issued "Guidelines for treatment of renal injury during cancer chemotherapy 2016, Clin Exp Nephrol. 2018; 22(1):210-244". Some committee members would be willing to participate in this conference.

Paul Stevens (KDIGO Executive Committee)

This is an enormous scope. First overarching question I would ask is, what do we intend to achieve from this controversies conference and secondly, who is the intended audience for the output(s) from this controversies conference? There are also some overlapping questions in the suggested breakout groups and I wondered whether you might consider changing the

groups slightly so that you have a Breakout Group called "Kidney Function Considerations in Onco-Nephrology" In this breakout group include questions 1, 7, 8, 12, 13,15 & 17 from "Kidney Problems in Haematology" and questions 2,3, 8 & 12 from "Kidney Impairment and Solid-Organ Malignancies" and then reordering the questions so that the questions flow from awareness of kidney function to measurement and monitoring of kidney function through to prevention of nephrotoxicity and AKI. If we can only have 4 breakouts then consider replacing "Kidney Impairment and Solid-Organ Malignancies" with "Kidney function considerations in Onco-Nephrology"

Kenar Jhaveri (Zucker School of Medicine at Hofstra/Northwell)

How does one define HSCT-TMA and how to recognize early signs of this entity? What are the treatment strategies that can employ both in adults and kids?

I think KDIGO should have a separate break out on chemotoxicities, check point toxicities and targeted therapy toxicities and immunotherapy toxicities and not lumped in breakout session 2 This the bulk of our consults and we need good guidelines for each one of the common chemos and how TO MANAGE the toxicities Cisplatin MTX Ifosfamide Gemcitabine EGFR inhibitors VEFG inhibitors BRAF inhibitors PD1 inhibitors CTLA4 inhibitors CART therapy For example: Gemcitabine induced TMA- data on pheresis, holding drug, complement inhibitors For PD1 inhibitors, how long steroids, if steroid resistant what to do, when to restart the pd1 inhibitor, etc.

Rumeyza Turan Kazancioglu (Bezmialem Vakif University)

Dear all thanks for the overview. I could suggest one more topic to the nephrology part where I think the role of new cancer drugs on proteinuria should be discussed also. Thank you

Priscila Goncalves (Northwell Health)

I am a medical oncologist who works with drug development and also work closely with the Nephrology team at our institution. Topics that I think would interest both specialties are:

- discussion oncology renal dysfunction trials and how nephrologists and oncologists can and should work together
- treatment of cancer patients on dialysis and renal dysfunction

- immunotherapy renal side effects (as oncologists are more and more using immunotherapy agents)
- treatment of renal transplanted patients
- including discussion of data of treatment with immunotherapy agents
- "what the nephrologist wants the oncologist to know"

Happy to be part of any discussion.

Cibele Rodrigues (Pontifícia Universidade Católica de São Paulo)

Agree with the scope. Maybe it's necessary to include: 1) specific breakout group of pediatric onco-nephrology and 2) palliative care in patients with cancer and kidney disease and ethical issues in RRT (initiation and withdrawal) in cancer patients.

Mitchell Rosner (University of Virginia)

First and foremost, this is an excellent document with a great background and extensive scope of work. Here are my detailed comments:

Group 1: AKI and Hematology
1. Tumor lysis syndrome is not unique to hematological malignancies and could be included as a more general topic and not restricted to this group.
2. The role of plasma exchange is an interesting topic
3. A more general issue for patients undergoing HSCT is the risk of worsening kidney function or dialysis if they have pre-existing CKD. How do we assess this risk?
4. Assessment of kidney function should also include: imaging and proteinuria determination
5. I would suggest reorganizing this questions as such:
    a. Assessment of Kidney Function in the Patient with Hematological Malignancies
    b. Assessment of Kidney Function in the Patient undergoing HSCT
    c. Monoclonal Immunoglobulin-Mediated Kidney Diseases
    d. Other Kidney Diseases Associated with Hematological Malignancies
    e. Pharmacological issues in these patients
    f. Protection of kidney function in these patients

Group 2
1. CAR-T cell therapies are not used in solid organ cancers and should be included in group

2. The other topics are great and highly relevant. Some overlap with group 3 exists.

Group 3
1. Need to include the role of the nephrologist both pre-treatment and post-treatment as this is critical in managing resulting CKD or changes in kidney function, and drug toxicity
2. The issue of CKD progression and management post-RCC surgery should be included
Group 4
No additional comments

Mona Alrukhaimi (Dubai Medical College)

Excellent. Just to add the role of high cut off HD in the management of multiple myeloma.

Kathleen Nicholls (Royal Melbourne Hospital)

Thank you for the comprehensive plan. I wondered about adding a discussion of the genetics of increased susceptibility to RCC e.g., VHL, BHD etc

Lesley Inker (Tufts Medical Center)

I suggest adding discussion about the exclusion of patients with CKD from most cancer trials. Because of this, we do not have sufficient information on the efficacy and safety of drugs in the CKD population. Relevant to this discussion is the methods used to estimate GFR for inclusion. The inconsistent methods used also leads to confusion and potentially discrimination.

Ben Sprangers (University Hospitals Leuven)

Dear Jolanta and Camillo: First of all thank you for this wonderful initiative to host the KDIGO Controversies Conference on Onco-Nephrology. As you know onco-nephrology is a topic that is very dear to me as I believe nephrologists have an important role to play in this area. But in order to do so we have to make sure that nephrologists are educated well so they can bring added value to the oncologic team. Therefore I believe education and guideline development is of the utmost importance. In the past I have been involved in the Cancer-Kidney International Network (together with Vincent Launay-Vacher) and have co-written a core curriculum article

on onco-nephrology in AJKD. I sincerely hope that this Controversies Conference will result in a KDIGO guideline regarding onco-Nephrology and I am very interested to contribute to this. I believe one of the major things these guidelines should encompass is development of recommendations regarding evaluation and use of chemotherapeutic drugs, targeted therapies in patients with CKD and transplantation, and providing dosing recommendations based on existing evidence in patients with CKD (including different dialysis modalities).
In addition, I have some potential additional topics for the different breakout groups:

Group 1: optimal diagnostic approach in patients with monoclonal gammopathy and renal disease (definitive, probable, potential MGRS) - role of laser microdissection/mass spectrometry in the diagnosis of MGRS - different free light chain assays and the role of FLC in diagnosis/monitoring of MGRS

Group 2: screening in dialysis patients: difference between patients on the transplant waiting list and patients not listed - dose recommendations for chemotherapeutic drugs in patients with CKD

Group 4: I believe 3.9 is of utmost importance as we are very often faced with this question – use of checkpoint inhibitors and other targeted therapies in transplant recipients Very much looking forward to this meeting and dedicated to actively contribute to its success. Best regards! Ben

Hideki Ishii (Nagoya University)

Cardio-Oncology has been now featured. CKD is sometimes one of comorbidities in such subjects. Left ventricular functions may be also reduced, therefore, cardiac functions as well as pericardial effusion should be also evaluated. Anti-cancer agents directly induce not only nephrotoxity but also cardiotoxity, In addition, cardiotoxity directly and/or indirectly affect renal function. Please discuss these points at the meeting.

Vladimir Tesar (Charles University, Prague)

Breakout Group 1: question 2 I would change to wording appropriately: Is there a role for plasma exchange and/or the use of dialysis with high cut-off membrane in the management of multiple myeloma cast nephropathy? Another suggestion: What patients with AL amyloidosis

should be treated with bortezomid, immune modulators, or autologous bone marrow transplantation? Hypercalcemia of malignancy should be specifically discussed

Breakout Group 2: I would divide very broad question 4 into: nephrotoxicity of chemotherapy and radiotherapy and nephrotoxicity of targeted treatment. Nephrotoxicity of bisphosphonates frequently used in cancer should be also discussed

Breakout Group 3: the main question is, in my opinion: What should nephrologist now about the treatment of kidney cancer, or how the role of nephrologist in the treatment of kidney cancer could become more important?

Mark Perazella (Yale University School of Medicine)

The Scope of Work presented is quite broad and we are not likely to cover all of the topics. In each section, it is probably best to arrange by the following: 1) estimation of kidney function/eGFR/mGFR in the various cancers/disease categories (Heme malignancies, Solid cancers, RCC, and Transplant malignancies); 2) diagnostics available (biomarkers, imaging, tissue studies, etc) for the various cancers/disease categories (Heme malignancies, Solid cancers, RCC, and Transplant malignancies); 3) Prevention and treatment of AKI and CKD for the various disease categories (Heme malignancies, Solid cancers, RCC, and Transplant malignancies); and 4) Renal drug toxicities observed in the various cancers/disease categories (Heme malignancies, Solid cancers, RCC, and Transplant malignancies).

Ala Ali (Nephrology and Renal Transplantation Centre, Baghdad, Iraq)

1. The issue of paramount importance is the awareness of oncologists and hematologists to the issue of renal function, Cr, eGFR, and important electrolytes prior to embarking on chemotherapy.

2. Do we need measured GFR, OR an eGFR? MDRD orbCKD-EPI? Cr vs.CYS-C or both?
3. Do we need to consider special therapeutic targets of CNIs in recipients oh allogenic stem cell transplant?

4. Specific entity about the use of cisplatin and related compounds at low GFR!

5. Do we need to consider a specific form of ESA for the management of anemia in the context of malignancy?

6. More awareness for cancer screening in cases of GEN would be needed specially in developing countries!

7. What about the risk of malignancy transformation of acquired cystic disease in ESRD patients?
8. When to say no to RRT in advanced malignancy to decrease patients misery?

9. Should we start de novo mTOR inhibitors in patients at risk of malignancy at the time of transplantation or if they've already treated for cancer prior to transplantation?

10. Is there any difference between dose management of renal those of everolimus 1 mg in renal transplantation and 10 mg doses used in other malignant diseases and how this affects renal function?

Eisei Noiri (The University of Tokyo Hospital)

Breakout Group 1: Kidney Problems in Hematology
1. How do we recognize and prevent tumor lysis syndrome? We see more often in Burkitt lymphoma and ALL. It will happen starting tumor therapy. We can partially expect the tumor burden by laboratory data (Igs and UA Ca, etc). We could prescribe allopurinol or rasburicase and facilitate hydration with alkalization.

2. Is there a role for total plasma exchange in the management of multiple myeloma cast nephropathy? Yes, for the control of disease activity. We will prescribe PEx and DFPP. The most common cause of severe acute kidney injury in multiple myeloma patients is tubulointerstitial nephropathy, which results from very high circulating concentrations of monoclonal immunoglobulin free light chains (FLC). In the setting of AKI, an early reduction of serum FLC concentration is related to kidney function recovery. Pl also take a look at my text book "Concise Manual of Apheresis Therapy" from Springer. Our short review in "Scientific World Journal. 2013 Oct 27;2013:487285. doi: 10.1155/2013/487285."

3. How do we optimally manage calcineurin inhibitors in the recipients of allogeneic stem cell transplant? Monitoring at trough.

4. How do we increase the awareness and recognition of renal amyloidosis? NS, renal biopsy, biopsy of subcutaneous adipose, sometime biopsy from stomach, hypotension, ECG low voltage, macroglossia, etc.

5. Is a renal biopsy required to initiate chemotherapy in suspect immunoglobulin cast nephropathy? Not necessary if diagnosed with other information. This is because of hematological abnormality often cause bleeding issue after renal biopsy.

6. How do we manage cancer pain during the opioid crisis while avoiding renal toxic agents? Indwelling catheter to myeloid space.

7. How do we educate oncologists to ensure correct dose adjustments of chemotherapy proportionate to GFR? PharmD involvement will improve the situation. It is not good situation like “Cancer totally gone, and patient passed”.

8. When a patient is newly diagnosed with cancer, what is the minimum renal testing appropriate prior to initiating therapy? Serum creatinine, cystatin C, proteinuria, urine L-FABP, NAG, urinalysis

9. Which patients with monoclonal gammopathy of renal significance should be offered treatment? One of initial recommendation is DFPP and PEx for the control of disease activity to attain the efficacy of chemotherapy. See my book “Concise Manual of Apheresis Therapy” from Springer.

10. When are patients with myeloma and amyloidosis on dialysis candidates for kidney transplantation?

11. What is the appropriate chemotherapy selection for treatment of monoclonal gammopathy of renal significance? Melphalan and PSL.

12. How should one best estimate kidney function in hematopoietic stem cell transplant (HSCT) patients? HSCT related kidney diseases are keen interest to both patients and physicians. Serum creatinine level is not reliable marker to such patients, because muscle mass and hydration state often cause mis-reading at the small change of serum creatinine. And therefore, the alternative evaluation is necessary. I would prefer to use cystatin for repeated evaluation which is more accurately follow Tc-DTPA than serum creatinine in the recent clinical study. But for more accurate evaluation, I would consider radioisotopes (Tc-DTPA and Tc-MAG3) and inulin clearance.

13. What is the optimal dosing of cytotoxic agents in patients in eGFR < 30 ml/min/1.73 m^2? PharmD has table for suggested dose for each cytotoxic agent in our institute.

14. What are the roles of high cutoff membranes and new sorbent devices (CytoSorb) in HSCT patients? CytoSorb has not been reimbursed in Japan yet. The molecular range of sepsis, taken care by CytoSorb, can be cleared by CRRT which is much more reasonable expense. PMX-DH is often prescribed in Japan to sepsis after chemotherapy and shows efficacies. But it is not so surprising efficacy that the number of reported manuscript is very small especially in English. As a reference, the efficacy of PMX-DH to sepsis after bone marrow transplantation instead of CytoSorb was reported at Case 1 of Clin Nephrol 81:67-70, 2014. Similar reports can be found in sepsis after chemotherapy to other hematological disorders and solid tumors in Japan.

15. Is there a potential of renal toxicity from alternative treatment means?

16. How should one monitor kidney function and assess renal injury during the course of HSCT treatment? We recommend prescribing urine L-FABP before treatment to know the susceptibility to AKI, because higher patients tend to develop AKI and show higher in-hospital death rate. L-FABP is reimbursed in JPN. L-FAPB POC is available for easy monitoring for the subclinical AKI.

17. How should one optimally balance efficacy of treatment and renal toxicity of drug treatments? Cancer treatment should be prioritized for eradication. Renal toxicity should come the second though we will consider the minimum effective dose to the kidney.

18. What are the pathomechanisms to CKD as a consequence of hematological cancers? Because the prognosis of hematological cancers has been not enough to evaluate CKD, there is not much data. We often see mild to moderate increase of serum creatinine with 1+ proteinuria or without proteinuria. This is often the chronic effect of cancer therapy which is inevitable. Unless nephrotic, kidney biopsy will be never done. In such case, FGS is often diagnosed.

19. Which hematological cancer patients with CKD can be treated with erythropoietin-stimulating agents (ESAs)? It is reportedly cancer cells often express EpoR (erythropoietin receptor). If EpoR not expressed and AKT is not over expressed, ESAs might be prescribed carefully. However, there is still concern to the potential of subclinical risk to thromboembolic disorder. It is reportedly dose dependent presumably due to the disease activity.

20. Are HSCT patients at increased risk for post-contrast AKI? Yes. In post HSCT, AKI is the highly risk to survival. So each contrast medium procedure should be considered its indication more carefully.

21. To dialyze or not: Is withholding dialysis a valid treatment option for hematological cancer patients? If hematologically equivalent to death, we will discuss with patient stopping dialysis therapy.

Romano Danesi (University of Pisa, Italy)

The coverage is comprehensive and well detailed. I have no suggestions for change/integration.

Lavinia Negrea (Case Western Reserve University, Cleveland, Ohio)

Agree with the proposed Scope of work.

Motoko Yanagita (Department of Nephrology, Kyoto University Graduate School of Medicine)

No. 7 and 13 of the Breakout Group 1 are about the rational dose adjustments of chemotherapy in patients with kidney dysfunction. There are no guidelines regarding cancer chemotherapy for patients in renal dysfunction, and the pharmacokinetics data are limited. There are recommendation of dose adjustments, but these recommendations are based on a small series of case reports and expert opinions. Pharmacokinetics data of the drugs based on therapeutic drug monitoring are warranted and the anti-cancer efficacy of the adjusted doses should be also monitored. Another point to be considered is the indication of chemotherapy. We organized multicentric case series analysis which recruits newly diagnosed cancer patients after induction of hemodialysis (HD) from 2010 to 2012 (674 patients) in Japan, and analyzed clinical practice variation in cancer treatment in dialysis patients. Part of the data is already published in ESMO Open this year (Funakoshi T, Matsubara T, Yanagita M et al. ESMO Open. 2018; 3(2):e000301.). Even in the drug for which dose adjustment is not recommended because of catabolism in the liver like 5-FU, catabolites are sometimes accumulated in dialysis patients, and cause toxicity (Nishikawa Y, Matsubara T, Yanagita M et al. Cancer Chemother Pharmacol. 2017; 79(3):629-633.). We can additionally analyze clinical questions from this Conference utilizing this cohort.

Breakout Group 2, No. 9 Cancer screening in dialysis patients For dialysis patients in the United States, routine cancer screening is not recommended unless the patients are on transplant list. However, not all patients can receive transplants. Moreover, the life expectancy of dialysis patients is improving, and the mortality rate due to cancer is increasing. If we discover the tumor in a resectable state by early detection, we can expect improved prognosis. We organized multicentric case series analysis which recruits newly diagnosed cancer patients after induction of hemodialysis (HD) from 2010 to 2012 (674 patients) in Japan, and analyzed clinical practice variation in cancer treatment in dialysis patients. Part of the data is already published in ESMO Open this year (Funakoshi T, Matsubara T, Yanagita M et al. ESMO Open. 2018; 3(2):e000301.). In Japan, cancer screening is routinely performed in each institute. In this analysis, time interval from HD start to cancer diagnosis was 73 months, and about 80% of the cancer patients were found to have resectable lesions, and more than 90 % of the HD patient with the resectable cancer underwent curative operation (manuscript in preparation): these data are significantly better than previous reports (Janus N et al. Ann Oncol. 2013; 24(2):501-7, Taneja S et al. Clin J Am Soc Nephrol. 2007; 2(5): 1008–1013). Of course, cost benefit balance should be considered, but cancer screening for those who assumed to benefit: those with good survival expectancy and those at a high cancer risk should be considered in addition to the candidates for transplantation. We can additionally analyze clinical questions from this Conference utilizing this cohort.

Additional comment about the rational dose adjustments of chemotherapy in patients with kidney dysfunction. In addition to the publication that I cited in my previous comment, we also published an abstract at ESMO regarding the pharmacokinetics data of oxaliplatin, which shows that the amount of L-OHP removal by dialysis was up to 10% regardless of the timing of L-OHP administration. https://doi.org/10.1093/annonc/mdx388.063 Additionally, since last year, we started “Onconephrology Expert Clinic” in our Oncology Center in Kyoto University Hospital. This expert clinic accepts kidney injury patients due to chemotherapy and molecular targeted therapy, as well as cancer patients with renal dysfunction. We discussed the choice of the treatment of these patients with oncologists regularly and the multidisciplinary approach improves the treatment of these patients.

Verônica Torres (São Paulo State Cancer Institute)

First of all, I would like to congratulate ISN and the Committee for the initiative. I´m nephrologist from the São Paulo State Cancer Institute for the last ten years. Our hospital is the largest cancer center in Latin America (affiliated of the São Paulo University, the most important academic institution in Brazil), admitting for treatment ~10,000 patients early. Eighty

percent of our patients have solid tumors. I would like to know if it´s possible for you to have one or two of our nephrologist at the event as listeners. I imagine that we could provide input from the reality of Latin America. I think the scope of topics is quite broad and certainly will bring unique opportunities for debate. I have the feeling these questions were built based on the scope of patients more frequently affected by hematology cancers than solid tumors, which does not represent the reality of the general, global population. I think that should be reassessed, if possible. I have a few suggestions that I did not see represented:

1. Tumor Lysis Syndrome: - Criteria for kidney injury in this context: it requires update according to our recent guidelines for AKI - Validation od biomarkers that might help in order to help in diagnosis (around 50% of our patients initiating dialysis in the ICU in consequence of sepsis, chemo etc fulfill the current criteria) - Dialysis: which dialysis modality, dose, strategy is most suitable - Use of sevelamer: is there a place? - The incidence in solid tumors that seems to be undereported in literature

2. Myeloma cast nephropathy: - Is there a place for high cut-off membranes?: position on the two recent clinical trials - How to estimate glomerular filtration rate in these patients?. When to order measured (radioisotopic, for example), clearance? - How to assess kidney impairment (AKI and/or CKD) that will fulfill the criteria of kidney dysfunction that would call for treatment in myeloma patients? And how to assess the impact on survival (current scores such as Durie-Salmon incorporate kidney function) - What is the best option to treat myeloma cast nephropathy with severe impairment, particularly in dialysis in the case bortezomib is not available (which is the crude reality of several countries in the world).

3. Lymphoma: - What is the real % of patients with kidney infiltration due to lymphoma? - How to assess GFR in these patients?

4. Cancer-related glomerulonephritis: -It is not even mentioned... - But it seems that the general idea that membranous glomerulonephritis is the most frequent pattern does not seem to be what we see in clinical practice. How to better assess that?. Necropsies surveys? - How and when indicate immunosuppressors to treat glomerulonephritis in cancer patients (which parameters can indicate those patients that would tolerate).

5. The topics on chemotherapy toxicity is too vague. Important questions related when suspend and reintroduce as well how to prevent important and frequent toxicities such as cisplatin, carboplatin, methotrexate, anti-VEGF drugs could be addressed. An important point is the use of renal replacement therapy as an instrument to help dealing with important, life-

threatening toxicity related to chemotherapy. There is literature in the case of methotrexate and iphosphamide that could be discussed.

6. Hypercalcemia: - Is there still a place for diuretics? - Which are the indications and the best moment for dialysis as treatment? - The role of new agents?

7. Obstructive uropathy: I do not understand. Urology issues seem to be largely under represented. One third of the consultations to the Nephrology Service in our hospital are in consequence of urology complications. Obstructive Uropathy is the most frequent event and there are several important gaps such as factors related to kidney recovery (when to define the patient as chronically dependent on dialysis), how to manage devices (nephrostomy and JJ catheters), the role of biomarkers and if any intervention could improve kidney function at diagnosis.

8. Kidney Cancer: There is nothing about the role of cryo/radio ablation as well the recent "radio"surgery or ablation through radiotherapy strategies that are also kidney/nephron sparing - Kidney function after nephrectomy: is there a role and timing to investigate prophylactic measures in high risk patients (aged, diabetes, arteriopathy): hydration, statins, etc pre-surgery? Similar way as contrast planning. - Assessment of the normal (non tumoral) histology by pathologists: necessary - How to assess and follow kidney function: when to use radioisotopic clearance? - When to assess relative kidney function pre-nephrectomy? (DMSA)

9. Bladder cancer: - How to assess and follow GFR: equation are not validated, - How to best manage (indicate reoperation or urinary diversion) in cystectomized patients which are a high risk group to develop CKD and lose kidney function over time. - There are specificities from these patients that should be highlighted. It´s unique opportunity to preserve - How to best manage complications such eletrolytic disorder, kidney stones.

10. AKI in the ICU: Cancer patients represent 20% of ICU patients in general ICUs worldwide and AKI is a frequent event. Dialysis is often prescribed. Some input on these patients would be welcome. Intensivist and Oncologist have been assessing these patients with great interest. They follow the trend of improved survival observed in cancer patients but we do not have recommendation in the case of dialysis modality, dose or the hit of the moment timing. We do not know it these aspects are relevant in cancer patients. Actually, AKI does not seem to be adressed in the offered scope. There is interesting, initial data on AKI biomarkers in cancer patients. Repeated AKI insults over time through cancer treatment are a major contribution to CKD in cancer population and this topic deserves further attention (AKI criteria, biomarkers, prognosis with focus in cancer related survival, not only general).

11. In the dark, undefined field of chemotherapy prescription in patients under chronic dialysis, it should be really valuable for the nephrology community offer advice or recommendation for drugs management or at least a position in which guidelines/reference should be followed.

12. A word in chronic dialysis patients with Thyroid Cancer that are admitted to iodotherapy: how to best manage these patients. Good luck in the event. Looking forward to read the final document.

Deepak Sharma (PVT)

Well-considered scope of work.

Francesco Iannuzzella (IRCCS-AUSL Reggio Emilia, Italy)

A number of points included in the Appendix seems to suggest that the use of chemotherapy in advanced CKD/ESRD is mainly a matter of dose/dosage adjustment. Please, consider some other aspects:

- dialysis modality/schedule/incremental vs standard treatment
- timing of dialysis initiation in ND CKD5 cancer patients candidable /sic/ to chemotherapy
- changes in chemotherapy protocols (not only dose or type, but also frequency and timing of drug administration) according to dialysis schedule
- the use of either hemodialysis or peritoneal dialysis as palliative treatment
- the concept of dialysis adequacy in this special population

Clarissa Havel (RPh-on-the-Go, BCPS)

The scope of work on oncology and nephrology will be helpful to all clinicians. Very useful discussions and questions.

Maria Jose Soler Romeo (Nephrology Research Group, Vall d'Hebron Research Institute (VHIR) and Nephrology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain)

In my mind it raised the following points:

Breakout Group 1: Kidney Problems in Hematology: **When should acute dialysis be started, early vs late?

Breakout Group 2: Kidney Impairment and Solid-Organ Malignancies: **Other interesting point. When should cancer patients be renal biopsied? **When and how should cancer-related hypercalcemia be treated? This should also apply to hematology problems. Cancer screening in patients with glomerulopathies: When and how should it be done? ***How should the cancer and immunosuppressive treatment be assessed? risks vs benefits?

Elena Zakharova (Moscow City Clinical Hospital n.a. S.P. Botkin)

Some additional topics for discussion:

1) Kidney problems in hematology - Diagnostics of monoclonal gammopathies of renal significance, crucial role of kidney biopsy - MPN-related glomerulopathy - do we diagnose and treat this condition

2) Kidney impairment and solid-organ malignancies - Do we know the spectrum of paraneoplastic nephropathies in solid-organ tumors?

3) Management and treatment of kidney cancer - Membranous nephropathy in patients with renal cell carcinoma - is it always secondary MN

4) Malignancy and kidney transplantation: Post-transplant lymphoproliferative disorders, including transplanted kidney lymphoma - epidemiology, role of transplant biopsy, treatment options

Rommel Bataclan (University of the East Ramon Magsaysay Medical Center)

Onco-nephrology has become an important aspect of our practice and it is about time to discuss specific aspects. I wish additional queries would include:
- Frequency of monitoring and screening of renal function regardless of oncologic condition
- How to distinguish donor-derived from a de novo Malignancy in post-KT patients?
- Alternative therapies in cancer with subsequent nephrotoxicity.

Daniela Niepel (Amgen)

It would be great if the proposal and topic of the controversies conference would lead to discussion related to the overall issue of bone health in MM/oncology patients including maybe the following:

Bone health in patients with preexisting renal morbidity (with or without renal osteodystrophy); ideally recommendation for a holistic approach including lifestyle measures and pharmacotherapy to protect bone while protecting renal function

Managing bone health in MM/oncology patients with or at risk of progressive renal morbidity: bone protection is a key element in MM; however, zoledronic Acid is considered nephrotoxic and is also not allowed to be administered in patients with CrCl<30ml/min

Also please consider complications from MM as defined by CRAB features: increased Calcium, Renal impairment, Anemia, Bone lesions)

Some key opinion leaders we recommend:

- Hematologist: Dr. Ihab Elhemaidi, NGH – Jeddah – KSA
- Hematologist: Dr. Mohammed Abu Haleeqa, SKMC – Abu Dhabi – UAE
- Dr. Mark Cook, Birmingham (has done work on myeloma, proteasome inhibition and renal insufficiency (national lead in this area)
- Dr. Karthik Ramasamy, Oxford

Zoran Paunic (Special Hospital for Haemodialysis, Fresenius Medical Care Belgrade)

Management of new cancers in ESKD/Dialysis patients (antineoplastic drugs frequently are not approved for this population); KDIGO attitude to ESA in dialysis patients with or after cancer treatment.

Na Qi (KBP Biosciences)

It is a content-rich conference. The onco-nephrology theme reminds me of a epidemiological link between ADPKD and caner. ADPKD is a genetic kidney disease, which is mostly caused by

the mutation of PKD1 or PkD2 gene. Although there are neoplastic cysts growth in ADPKD patients, studies showed that the morbidity of cancer is lower in these patients. Data from the Scientific Registry of Transplant Recipients, which contains information on all solid organ transplant recipients in the United States, were linked to 15 population-based United States cancer registries that included data on 50 different cancers. Cancer incidence was compared in PKD versus non-PKD renal transplant recipients, and incidence rate ratios adjusted for age, sex, race/ethnicity, dialysis duration, and time since transplantation were determined. The study included >10,000 kidney recipients with PKD and >100,000 without PKD. After multivariable adjustment, overall cancer incidence was found to be significantly lower in patients with ADPKD by about 16%–17%, suggesting that there is cancer protection associated with PKD. This was also found to be true for ARPKD, in a study that examined the incidence of colon cancer in unaffected carriers of a recessive PKHD1 mutation. Some researchers believed that high Myc levels and Cox-2 inhibition could be the reasons. As such, the unusual PKD biology may paradoxically promote neoplastic cyst growth while preventing progression to metastasis, leading to lower cancer incidence. It will be important in the future to better understand these cancer-related signaling mechanisms for the design of PKD-specific antiproliferative therapies that will slow cyst growth and kidney enlargement without inadvertently opening a Pandora's box of metastatic cancer. Maybe you could add a topic base on this. Thank you.

Youssef Farag (Akebia Therapeutics, Inc.)

Dear KDIGO - Please see below my comments on the KDIGO Onco-Nephrology Scope of Work. I am interested in actively participating and contributing more in the KDIGO Onco-Nephrology conference and workgroup. Thank you very much. Sincerely, Youssef

Group 1: Kidney problems in hematology
• What is the epidemiology, risk factors, and survival of kidney failure in hematologic malignancies? • What are the histopathologic features of kidney failure across different hematologic malignancies? • Is there a need to validate the GFR estimating equation(s), most commonly CKD-EPI equation, among patients with hematologic malignancies? Do we need to validate the equation in different subpopulations (sickle cell disease, MDS, stem cell transplant etc…)? • What is the epidemiologic characterization of malignancy and metastasis among patients receiving ESAs? • Does treating patients with hematologic malignancies with ESA would provide incremental improvement in quality of life? • What are the risk factors for incident cancers (either solid organ or hematologic) among patients with CKD (by stage) and on dialysis? Specific hematologic malignancies: • Multiple myeloma (MM) o Antibodies deposited in the kidney causing cast nephropathy and nephrotic syndrome: § Management is focused on

treating MM but not reversing, improving, or stabilizing kidney damage. § In addition, there is no evidence of epidemiology, pattern or prognosis of renal impairment in MM patients. • Transthyretin amyloidosis o What are the best management strategies for kidney failure in transthyretin amyloidosis, especially after the approval of the latest Pfizer drug, Tafamidis? o What is the summary of evidence recommending simultaneous liver-kidney transplantation for patients with transthyretin amyloidosis? • Bone marrow transplantation: o Eculizumab, a recently approved drug to preserve kidney function in Atypical Hemolytic Uremic Syndrome has been suggested to also preserve kidney function in patients with Thrombotic microangiopathy (TMA) occurring after allogeneic hematopoietic stem cell transplantation (HSCT). No formal evidence generation or recommendation is available for the use of eculizumab in HSCT recipients. • Myelodysplastic Syndrome (MDS): o What are the risk factors for kidney failure and prognostic survival of patients with MDS? • Tumor lysis syndrome: o What are the prognostic factors for the success of the use of raspuricase in the treatment of tumor lysis syndrome? • Sickle cell disease: o What are the best management strategies in patients with sickle cell disease who develop renal papillary necrosis or FSGS?

Group 2: Kidney problems in solid organ cancer

• Rephrasing of Q1: What is the epidemiology and risk factors of CKD in different solid organ tumors? • Rephrasing of Q5: What is the epidemiology and risk factors of hypocalcemia in cancer patients? Does it differ by cancer type, demographics, treatment strategies? • Rephrasing of Q14: What is the epidemiology and risk factors of contrast-induced AKI in cancer patients? • What are the prognostic factors for success and survival of patients who are treated for cancer-related hypercalcemia?

Group 3: Kidney cancer

• Does the recent increase in RCC incidence reflect true increase in incidence, overdiagnosis, early diagnosis, or improved diagnostic modality over time? If it is true increase, what are the emerging risk factors that led to that? • What are the risk factors for the development of CKD and metabolic syndrome of unilateral nephrectomy in RCC patients? • What is the long-term prognosis of patients with mRCC who received chimeric antigen receptor (CAR) T-cells? What are the risk factors for survival?

Group 4: Cancer in kidney transplant

• What is epidemiology and risk factors for incident renal and non-renal cancer among kidney transplant recipient?

Elerson Costalonga (Cancer Institute of São Paulo, University of Sao Paulo)

Dear, first of all, congratulations for this initiative. The oncology population is growing and the interplay of CKD and Cancer has to be deeply studied. As an Onco-nephrologist working in a 500 bed Oncology Hospital (Cancer Institute of Sao Paulo), I have read with great interest the scope of work for public review. I have some suggestions and questions, and I sincerely hope that these suggestions could contribute for the development of your work. Comments:

Breakout Group 1: Kidney Problems in Hematology

1. How do we recognize and prevent tumor lysis syndrome? The most widely used diagnostic criteria for tumor lysis syndrome (TLS) are those proposed by Cairo et al in 2004. Based on this classification, TLS can be defined as laboratory TLS, when TLS is clinically silent and only detected through laboratory work up, and clinical TLS, when laboratory TLS is complicated by the clinical manifestations mentioned above. However, the application of these criteria should be done with some caveats regarding kidney function. First, in the Cairo-Bishop criteria the threshold to detect acute kidney injury is one creatinine level above 1.5 times ULN. So, patients with more subtle, but clinically significant changes of the serum creatinine could not be diagnosticated as Clinical Tumor Lysis Syndrome. Further, the criteria may be less specific for detecting TLS in patients with moderate kidney disfunction. Hyperuricemia, hyperphosphatemia, hypocalcemia, and hypercalemia could be the present at any patient with moderate to severe kidney disfunction, despite the underlying etiology. For example, at our institution, almost 30% of patients with AKI AKIN II or III, without TLS , evaluated by a nephrologist fulfilled the Cairo-Bishop Criteria (data not published). So, I think the we need to improve the diagnosis criteria for TLS in the clinical setting of patients with kidney disfunction. Regarding the therapy with rasburicase, due to the lack of evidence of benefit in the prevention of hard endpoints (p ex dialysis), it will be very interesting if the comitee could draw some indications of when to use this treatment. 2. Is there a role for total plasma exchange in the management of multiple myeloma cast nephropathy? Beyond the role for plasma exchange, I think that will be of value, if the panel of experts also discussed the role of high Cut-off hemodialysis in this situation. 5. Is a renal biopsy required to initiate chemotherapy in suspect immunoglobulin cast nephropathy? At our center, we do not routinely perform kidney biopsy before the chemotherapy when there is a suspect of cast nephropathy. In a patient with myeloma multiple and kidney dysfunction, we think that the find of a non selective proteinuria with predominance of gamaglobulin in the urinary protein electrophoresis, is sufficient to diagnosis cast nephropathy. Obviously, some patients will require kidney biopsie. Further, the prognostic role of kidney biopsy, in this clinical situation, are not well established. 6. How should one monitor kidney function and assess renal injury during the course of HSCT treatment? Transplantation HSC has been successfully developed as a part of treatment

protocols for a large number of clinical indications, and cryopreservation of both autologous and allogeneic sources of HSC grafts is increasingly being employed to facilitate logistical challenges in coordinating the collection, processing, preparation, quality control testing and release of the final HSC product with delivery to the patient. Direct infusion of cryopreserved cell products into patients has been associated with the development of adverse reactions, ranging from relatively mild symptoms to much more serious, life-threatening complications, including acute kidney injury associated with hemoglobnuria. In many cases the cryoprotective agent used — which is typically dimethyl sulfoxide (DMSO), is believed to be the main causal agent of these adverse reactions So, further the traditional approach to monitoring kidney function, I would like to point out the importance of recognizing haemoglobinuria as a cause of AKI that should be monitorized in this scenario.

Breakout Group 2: Kidney Impairment and Solid-Organ Malignancies
There is an interplay between chronic kidney disease (CKD) and cancer. CKD and end stage kidney disease (ESKD) are known risk factors for cancer as well as the cancer progression and its treatment can lead to the development of CKD. With the improvements in the cancer treatment, patients will be living longer with cancer and a continuing rise on the rate of CKD is expected in this population. In spite of the burden of CKD in cancer patients, as far as we know, no study had studied more deeply CKD in this population regarding CKD issues such as etiology, the impact of traditional risk factors (hypertension, dyslipidemia, albuminuria and diabetes), complications of CKD and predictors of outcome. So, I would like to suggest the discussion about how to manage blood pressure, dyslipidemia, bone mineral disease, and glycemic control in the patient with cancer and CKD.

Thank you for this opportunity to contribute to yours outstanding work.
Best Regards
Elerson Costalonga
Medical Coordinator of Onco-nephrology Division
Cancer Institute of Sao Paulo
University of Sao Paulo, Brazil

Patricia Abreu (UNIFESP: FEDERAL UNIVERSITY SÃO PAULO – BRAZIL)

Dears KDIGO colleagues, thanks for the invitation KDIGO Onco-Nephrology will improve, substantially, the care of patients with malignancy My comments: 1- i would like to suggest how do hematologist could recognize, early membranous nephritis and crescentic GN 2- should we considered ESA for patients with malignancy in the past? Is cystatin C better than creatinine to estimate GFR in elderly with malignancy? Best regards! Patrícia Abreu

Joanna Rowinska (Medical University of Warsaw)

I'm a clinical nephrologist working in a big teaching hospital, affiliated with Medical University of Warsaw. We cooperate with our hematologists and the nephrological challenges in modern onco-hematology are of utmost importance to us. We have many patients with myeloma on chronic dialysis, and acute AKI patients with tumor lysis syndrome. The scope of the Conference is so wide that it may turn out to be difficult to cover all mentioned issues. However in/for breakout group 1: • The approach to hypercalcemia of malignancy should be definitely added, since it is very common (20-30% of all malignancies), has vital consequences and the treatments are not free from nephrotoxicities. Obviously it applies not only to hematology but also to solid cancers, however we have many other overlapping issues and all of them, initially drafted in the breakout groups, will be rediscussed in a larger forum during the second part of the meeting. That should be OK. • With the advent of new, more effective anticancer therapies the tumor lysis syndrome has probably changed a lot in its every aspect and may deserve a bit broader discussion, with its definition, risk factors, and treatment of its established form. • I would change the question 2 to" Is there a role of extracorporeal removal of free light chains in myeloma cast nephropathy? " to cover all: plasmapheresis, high cut-off dialysis and adsorption techniques. Best regards

Pierre Ronco (Pierre and Marie Curie University)

Breakout Group 1: Kidney Problems in Hematology
Q 2. Is there a role for total plasma exchange in the management of multiple myeloma cast nephropathy?

- Before that, what are the supportive measures that should be taken to correct prerenal azotemia in those patients?
- Is there a role for high-permeability membrane in patients who require dialysis; in non-dialyzed patients with CKD stage 4 and 5?

Q 4. How do we increase the awareness and recognition of renal amyloidosis?

- Amyloidosis in general, not only renal

Q 5. Is a renal biopsy required to initiate chemotherapy in suspect immunoglobulin cast nephropathy?

- What are the best combinations of chemotherapy in this setting? Waht are the aims?

Q 8. When a patient is newly diagnosed with cancer, what is the minimum renal testing appropriate prior to initiating therapy?

- This question is also (more) justified for non hematological tumors

Q 9. Which patients with monoclonal gammopathy of renal significance should be offered treatment?

- by definition ALL

Q 10. When are patients with myeloma and amyloidosis on dialysis candidates for kidney transplantation?

- rather which patients are eligible for dialysis and transplantation?

Q 11. What is the appropriate chemotherapy selection for treatment of monoclonal gammopathy of renal significance?

- more specifically, which investigations should be performed to identify the underlying plasma cell or B-cell clone?

Q 17. How should one optimally balance efficacy of treatment and renal toxicity of drug treatments?

- I think this question is too general. It should be asked for each type of malignancy

Q 21. To dialyse or not: Is withholding dialysis a valid treatment option for hematological cancer patients?

- this question rather applies to non hematological solid tumors because of the wide range of more and more efficient chemotherapies/biotherapies (monoclonal antibodies) in pts with hematologic malignancies

Breakout Group 2: Kidney Impairment and Solid-Organ Malignancies

Q 1. What is the epidemiology of CKD in solid-organ tumors?

- a major issue here is the definition of CKD and how proteinuria and hematuria are assessed

Q 3. How is kidney impairment (GFR and biomarkers of cell damage) best measured in cancer patients?

- see above for proteinuria and hematuria

Q 8. What are the key renal investigations for patients with solid-organ malignancy?
Consider:
a. At cancer diagnosis
b. During oncological treatment
c. During follow-up

- very much dependent on the type of treatment

Q 10. Cancer screening in patients with glomerulopathies: When and how should it be done?

- perhaps be more specific because the screening depends on the type of glomerulopathy