Global Action. Local Change.

KDIGO Controversies Conference on Onco-Nephrology

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Milan, Italy

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask conference participants to determine what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline efforts and other times they highlight areas for which additional research is needed to produce evidence that might lead to guidelines in the future.

Background

In the 21st century, patients with malignancy make up a growing number of the subjects seen for nephrology consult and/or critical care nephrology services. The outstanding progress in the therapy of malignancy presents new possibilities and challenges for both nephrologists and medical oncologists. It is important for nephrology services to be acknowledged and to take an active participation in the care of oncology patients. In addition, nephrology services need to better understand the biology of malignancy and its treatment in order to become a valuable part of the teams working to yield the best possible outcome for cancer patients.

The links between kidney disease and malignancy were observed quite some time ago. However, it was only recently that their importance was recognized and a new subspecialty in nephrology, namely 'onco-nephrology' was established [1]. Chronic kidney disease (CKD) is often diagnosed in the general population [2], however, its

incidence and prevalence among patients with malignancy is not extensively studied and data are limited. Half a century ago, increased incidence of cancer in CKD patients was discussed by Sutherland *et al.* [3] and other reports also linked CKD with an increased incidence of cancer [4-10].

A plethora of renal problems may be found in patients with malignancy. They may influence not only their short-term outcomes but also the adequate treatment of the underlying oncological problem. Thus, all kidney-related issues pose an important challenge for both oncology and nephrology specialities. Indeed, the incidence rates for many malignancies are increased and the amelioration in cancer mortality, due to more effective chemotherapy including targeted drugs and treatment with stem cells, has resulted in a rise in the cancer survivors' population [12]. Some of these survivors develop acute kidney injury (AKI) or CKD due to either the cancer itself and/or its therapy [13]. The kidneys may thus be directly or indirectly damaged by the malignancy or by one or more of the novel therapeutics that prolong lives, however at the cost of developing AKI or CKD.

In addition, multiorgan failure may be also seen in cancer patients. As a consequence, they may require intensive care unit (ICU) care and kidney replacement therapy (KRT). In the setting of advanced malignancy complicated by multiorgan illness, the appropriateness of aggressive treatment in ''futile situations'' and the role of palliative therapy remains an open question. Thus, the care for oncology patients has become more specialized and complicated, requiring collaboration among nephrology, medical oncology, critical care, and palliative care. The question of persistent therapy (e.g., continuation of KRT in advanced malignancy) vs. end-of-life care is also one that more clinicians are facing today.

Relevance of the topic and the conference

The prevalence of both cancer and kidney disease is high and as such requires awareness from both oncologists and nephrologists concerning new cancer treatments and their potential adverse effects on kidney function. Therefore, the necessity of such

multidisciplinary experts calls for the need of a new subspecialty field of onconephrology.

Increased incidence of CKD, in particular in the elderly, is of utmost concern. Many antineoplastic agents are cleared primarily by the kidneys as unchanged drugs or active metabolites. Therefore, a decline in kidney function can potentially lead to alterations in pharmacokinetics, resulting in elevated blood levels of the drugs and increased toxicity. It has been shown that a remarkable number of CKD subjects treated with chemotherapy require dose reduction in case of CKD, but they are not administered the appropriate adjusted dose [14]. Thus, it should be stressed that CKD is an under-recognized problem in the oncology population and estimated glomerular filtration rate is to be assessed simultaneously, not only in oncology wards but also in every department. This is due to the fact that patients are getting older, exhibit more comorbidities, are administered with more potentially nephrotoxic drugs and undergo more potentially nephrotoxic procedures such as percutaneous coronary interventions or CT with intravenous contrast agents etc. [15] It is of paramount importance to be aware of the kidney function in patients receiving potentially nephrotoxic agents and to monitor their kidney function regularly before each course of chemotherapy. Oncologists should adjust the dose of cytotoxic drugs according to actual kidney function. Especially in CKD patients with impaired kidney function treated with nephrotoxic chemotherapeutic agents, concomitant drugs should be carefully evaluated (e.g., NSAIDS). They should be avoided, if possible, as they may contribute to the nephrotoxicity of chemotherapeutics.

Conference Overview

To this end, this KDIGO conference on onco-nephrology will gather a global panel of multidisciplinary clinical and scientific expertise (e.g., nephrology, oncology, intensive care, hematology pharmacology, etc.) that will identify key management issues in nephrology relevant to patients with malignancy. It is understood that the development of newer and more effective cancer treatments has led to an increasing number of cancer survivors but unfortunately many of these treatments can also be nephrotoxic.

Therefore, prevention, early detection, long-term monitoring and treatment of ensuing problems in these patients is a growing need in this population.

The objective of this conference is to assess our current state of knowledge related to AKI and CKD arising from malignancy and its associated treatments and to understand the management of malignancy after kidney transplantation. Care for oncology patients has become more specialized and complicated, requiring collaboration among nephrologists, oncologists, intensivists, and palliative care specialists. The remarkable advances in cancer management present new opportunities and complex challenges for the oncology and nephrology communities. It is essential for nephrologists to be informed and actively involved in certain facets of cancer care and a better understanding of the rapidly evolving field of cancer biology and its therapy is required for nephrologists to become a valuable member of the cancer care team and to provide the best nephrology care possible.

Drs. Jolanta Małyszko (Warsaw Medical University, Warsaw Poland) and Camillo Porta (IRCCS San Matteo University Hospital Foundation, Pavia, Italy) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. Invited participants and speakers will include worldwide leading experts who will address key clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a position statement that will help guide KDIGO and others on therapeutic management and future research in this area.

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APPENDIX: SCOPE OF COVERAGE

Breakout Group 1: Kidney Problems in Hematology

1. How do we recognize and prevent tumor lysis syndrome?
2. Is there a role for total plasma exchange in the management of multiple myeloma cast nephropathy?
3. How do we optimally manage calcineurin inhibitors in the recipients of allogeneic stem cell transplant?
4. How do we increase the awareness and recognition of renal amyloidosis?
5. Is a renal biopsy required to initiate chemotherapy in suspect immunoglobulin cast nephropathy?
6. How do we manage cancer pain during the opioid crisis while avoiding renal toxic agents?
7. How do we educate oncologists to ensure correct dose adjustments of chemotherapy proportionate to GFR?
8. When a patient is newly diagnosed with cancer, what is the minimum renal testing appropriate prior to initiating therapy?
9. Which patients with monoclonal gammopathy of renal significance should be offered treatment?
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?

12. How should one best estimate kidney function in hematopoietic stem cell transplant (HSCT) patients?

13. What is the optimal dosing of cytotoxic agents in patients in eGFR < 30 ml/min/1.73 m^2?

14. What are the roles of high cutoff membranes and new sorbent devices (CytoSorb) in HSCT patients?

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?

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

18. What are the pathomechanisms to CKD as a consequence of hematological cancers?

19. Which hematological cancer patients with CKD can be treated with erythropoietin-stimualting agents (ESAs)?

20. Are HSCT patients at increased risk for post-contrast AKI?

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

Breakout Group 2: Kidney Impairment and Solid-Organ Malignancies

1. What is the epidemiology of CKD in solid-organ tumors?
2. Which are the main pathophysiologic causes and mechanisms of kidney impairment in solid-organ tumors?
3. How is kidney impairment (GFR and biomarkers of cell damage) best measured in cancer patients?
4. What are the nephrotoxicity of various oncological treatments (e.g., chemotherapy, radiotherapy, targeted therapy, immune-therapy, CAR T-cell therapy, bone targeting agents)?
5. Is hypocalcemia a relevant clinical issue in cancer patients?
6. When and how should cancer-related hypercalcemia be treated?
7. How should diagnosis and treatment of hyponatremia addressed in cancer patients?
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
9. Cancer screening in dialysis patients: Under which circumstances is it indicated? When it is, which exams should be done and how often?
10. Cancer screening in patients with glomerulopathies: When and how should it be done?
11. ESA and iron therapy in CKD patients with malignancy: Are the indications for treatment any different than those of CKD patients without malignancy? What is the appropriate hemoglobin target? What ESA dose should be considered? Which are the effects of iron and ESA treatments on survival in cancer patients?

12. Should ACE inhibitors/ARBs be used for slowing kidney disease progression in CKD and/or nephrectomized cancer patients?

13. Is prevention of post-surgical AKI different in cancer patients compared to non-cancer surgery?

14. Is contrast-induced AKI a relevant issue in cancer patients? Should CKD patients with cancer receive fewer contrast media CT scans? How can contrast induced AKI be prevented in CKD patients with cancer?

15. Ethics: Should the presence of cancer affect dialysis decisions (e.g., initiation and discontinuation)?

Breakout Group 3: Management and Treatment of Kidney Cancer

Epidemiology, prevalence, type of renal cell carcinoma (RCC)

1. Has the epidemiology of RCC changed in recent years?

2. What are the histological subtypes of RCC and underlying molecular characteristics?

Kidney function in RCC

3. What are the risk factors for impaired kidney function in RCC?

4. What is the significance of metabolism or smoking as risk factors for RCC?

5. Is CKD as a risk factor and/or prognostic factor for RCC? If CKD is a risk factor, at what stage of CKD is a risk factor (e.g., ESKD)?

Type of surgery (e.g., nephron sparing, nephrectomy) and its effect on kidney outcomes

6. Who are candidates for nephron-sparing surgery?

7. What is the role of cytoreductive nephrectomy in metastatic RCC (mRCC)?

New targeted therapies and renal side effects

8. What are the classes of targeting agents in the treatment of mRCC?

9. Is there an optimal sequence of targeting therapies in mRCC?

10. What is the impact of novel therapies on the outcome of mRCC?

11. What are the most frequent side effects of targeting agents in the context of renal toxicity and how can one ameliorate them?

Follow-up after surgery (urologist, oncologist, nephrologist or dedicated team)

12. What is the role of adjuvant systemic therapy in high-risk localized RCC?

Breakout Group 4: Malignancy and Kidney Transplantation

Epidemiology

1. What are the incidence rates of developing *de-novo* cancers in kidney transplant recipients compared with the general population?

2. What are the cancer mortality rates in kidney transplant recipients compared to the general population? What are the reasons for the increased risk of death?

3. What are risk factors for cancer in kidney transplant recipients and what are the potential mechanisms for cancer development after transplantation?

Donor-derived cancers

4. What is the incidence of donor-derived malignancy in kidney transplant recipients and how may these risks differ by cancer types?

5. What are the general recommendations for the prevention of malignant tumour being transmitted from organ donors to recipients?

6. In what circumstances can a donor with active or past history of malignancy be accepted for donation? What are the recommended guidelines?

7. What are the current strategies for reporting, screening and management of those at risk and had acquired the disease after donor transmission of cancer has occurred?

8. What are the short- and longer-term outcomes of recipients who developed a donor-derived cancer?

Recipients with a prior cancer history

9. In patients with a prior cancer history, what are the eligibility criteria for transplantation? What should be the duration of wait time from remission? How does it vary by cancer types?

10. What is the risk of cancer recurrence and the prognosis of those with recurrence? Does it vary by cancer type and other patient characteristics?

11. What are some of the methods we could use to predict and prognosticate cancer recurrence in at risk patients?

Cancer screening in kidney transplant recipients

12. Should cancer screening in kidney transplant recipients differ from implemented in general population?

13. What specific cancer types should we screen for in a transplant recipient?

14. What is the role of education in cancer protection?

Management of cancer after kidney transplantation

15. What are the optimal strategies for managing a transplant recipient with a prior cancer history (does/types of immunosuppression)?

16. What are the optimal strategies for managing a transplant recipient with cancer after transplantation (does/types of immunosuppression)? Does it vary by cancer type?

17. What are the limitations in cancer therapy in kidney transplant recipients?

18. What are the patient preferences in cancer treatment decisions?