ANSWERING REVIEWERS

Reviewer's code: 02650654

Position: Peer Reviewer

Academic degree: MD

Professional title: Associate Professor

Reviewer's country: Italy

Dear reviewer,

first of all, we are grateful for the very important comments, which were essential to the improvement of this manuscript. All suggested changes were made as described below:

1. **A table including the mains kidnwy damage from antineoplastic drugs with the most important syndromes. In the text, it is highlighted in yellow in the manuscript and it is located in the end of the document.**
2. **The terms "necrosis" and "apoptosis" were rewritten in their correct meaning, as suggested (highlighted in yellow in the manuscript document)**
3. **Various parts of the text were deleted in order to make the text more abbreviated and objective, as you suggested(highlighted in the figures below):**

#

The vascular endothelial growth factor (VEGF) is an essential growth factor that plays a key role in angiogenesis during embryogenesis, wound healing and tumor growth. It was first investigated as potential anticancer agent over the past few decades. ~~The proangiogenic effect of VEGF is mediated primarily through receptor tyrosine kinases defined as vascular endothelial growth factor receptor (VEGFR) on endothelial cells. Upon ligation and autophosphorylation of VEGFR, numerous intracellular signaling pathways are activated and mediate the effects of VEGF on endothelial cell survival and proliferation~~[110].

VEGF pathway inhibitors consists in two different approaches: VEGF ligand inhibitors, which are antagonists of the vascular endothelial growth factor receptor (VEGFR) and are represented by ramucirumab, bevacizumab, and aflibercept~~, thus preventing activation of the receptor~~; and small molecule tyrosine kinase inhibitors (TKIs) (ponatinib, sunitinib, regorafenib, sorafenib, cabozantinib, pazopanib, axitinib, vandetanib, cabozantinib, lenvatinib), which prevents the activation of the VEGFR intracellular domain[111].

In normal conditions, VEGF is produced by the podocytes and binds to its receptors found in glomerular and peritubular endotelium, as well as in mesangial

~~Since the TKIs have an anti-VEGF effect, similar renal effects can be seen with them as well.~~ Regarding TKIs, proteinuria and hypertension can be seen with their use. In addition, AKI and diabetes insipidus have been reported in clinical trials of vandetanib, although causality has not been proven. Decreased GFR during therapy has been reported with axitinib, sunitinib, and sorafenib, although renal failure is rare. Patients treated with lenvatinib may progress to renal failure or impairment, while regorafenib has been associated with several electrolyte abnormalities, including hypophosphatemia, hypocalcemia, hyponatremia, and hypokalemia[119,120]. Sorafenib and sunitinib have been associated with acute and chronic interstitial nephritis in case reports[121,122]. Sorafenib is also known to cause hypophosphatemia and hypocalcemia[123].

~~*Inhibitor of Bruton's Tyrosine Kinase*~~

The immune response generated by CPIs is complicated by a number of immune-related adverse events related to many different organs, including the kidneys[129]. AKI is a rare complication of checkpoint inhibitor immunotherapy, being mainly associated with ipilimumab/nivolumab combination therapy (4.9%) ~~than with monotherapy with ipilimumab (2%), nivolumab (1.9%), or pembrolizumab (1.4%)~~[130]. The most commonly reported underlying pathology is acute tubulointerstitial nephritis, but immune complex glomerulonephritis and TMA have also been observed[131]. There is also an association between CPIs treatment and electrolyte abnormalities, with hypocalcemia being the most significant. Discontinuation of

Interferon-alpha (IFN-α) activates ~~the immune system by promoting promotes effector T cell-mediated responses, including~~ interleukin-2 (IL-2) release, what leads to cancer cells killing[133]. Recombinant IFN-α can cause proteinuria, which can be in the nephrotic range and AKI, the histology is consistent with minimal change disease or focal segmental glomerulosclerosis[134,135]. Rarely, TMA is seen and in this situation prompt drug discontinuation is critical[136].

The peptide receptor radioligand Lutetium Lu 177-dotatate is a radiolabeled somatostatin analog with potential antineoplastic activities. Lutetium Lu 177-dotatate binds to somatostatin receptors ~~present on the cell membranes of many types of~~ expressed by various neuroendocrine tumor cells. Once the radioligand binds to that

Best regards,

Fabrício Freire de Melo

Professor, PhD

Reviewer's code: 00505755

Position: Editorial Board

Academic degree: PhD

Professional title: Senior Research Fellow

Reviewer's country: Japan

Dear reviewer,

the comment you made was useful and we are grateful for your crucial help. Your comment was very important to make this article more informative. The definition of nephrotoxicity of anti-cancer drug was added and highlighted in green. Furthermore, information in the figures and in the table of the manuscript also complement such a definition.

Best regards,

Fabrício Freire de Melo

Professor, PhD

Reviewer's code: 00731613

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's country: India

Dear reviewer,

thank you for the crucial comment about this manuscript. Your suggestion was crucial for improving the quality of this manuscript. Adjustments were made in order to make the manuscript more critical as you suggested. The mechanisms for prevention of chemotherapy induced nephrotoxicity, the risk factors for development of chemotherapy induced nephrotoxicity, and the mechanisms of treatment for chemotherapy induced nephrotoxicity were added and highlighted in blue in the manuscript.

Best regards,

Fabrício Freire de Melo

Professor, PhD