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The Use of Hemoadsorption in Cancer-Related Complications

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Abstract

Background: Patients with metastatic cancer are at risk of drug-related toxicity or disease-related complications leading to the development of organ failure such as rhabdomyolysis-associated acute kidney injury (AKI), liver failure, and multi-organ failure, often precipitated by endotoxinemia and sepsis. In cases of systemic hyperinflammatory response, mediated by cytokines, to specific treatment with CAR-T-cell therapy or in sepsis with or without the development of AKI, we do not have an effective and specific target molecule-oriented therapy. ***Summary:*** Over the past few decades, numerous experimental and clinical studies have investigated the efficacy of extracorporeal blood purification technologies in the treatment of specific indications like sepsis and septic shock. In this review article, our goal was to show the possibility of using different hemoadsorbers in specific indications in patients with cancer-related complications, their reported effectiveness in certain indications and the possibility of applying it to cancer patients not only as a last-stand therapy but as well as preventing the development of specific organ or multi-organ failure. ***Key Messages:*** Currently, multiple forms of extracorporeal blood purification are available that may have benefit in patients with cancer-related complications. Despite a strong rationale for extracorporeal blood purification, many physicians are still reluctant introducing hemoadsorption as a recommended routine due to still insufficient evidence, mostly as a result of inadequate numbers of published randomized controlled trials. Nevertheless, the application of hemoadsorption should be the same for cancer-related complications as well as it is for other patients because, in most cases, we aim to remove the same target molecules.

Introduction

The projection for new cancer cases and cancer deaths in the USA for 2024 by the American Cancer Society is 2,001,140 and 611,720, respectively [1]. Through 2021, overall cancer mortality continued to decline but the incidence of 6 of the top 10 cancers is still increasing. Ninety percent of all cancer deaths are due to metastatic disease. The majority of patients with metastatic disease are treated with systemic agents and/or radiotherapy, which can provide substantial benefit for many patients, prolong survival and improve symptoms but are typically not curative, and patients are unable to achieve long-term survival. In addition, it is well known that cytostatic drugs and radiotherapy show a low safety profile and severe side effects since they are not specific to tumor cells [2–4].

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Among these patients, hospital admissions are common, often due to infection, febrile neutropenia, and/or anemia [5]. Patients with metastatic cancer are also at risk for drug-related toxicity or disease-related complications, leading to the development of organ failure such as rhabdomyolysis-associated acute kidney injury (AKI) [6, 7], liver failure [8], and multi-organ failure often precipitated by endotoxinemia and sepsis [9] (Table 1). We have effective and established treatment modalities for some specific cancer-related complications like in liver failure the usage of therapeutic plasma exchange [10]. In cases of systemic hyperinflammatory response, mediated by cytokines, to specific treatment with CAR-T-cell therapy or in sepsis with or without the development of AKI, we do not have an effective and specific target molecule-oriented therapy. Only specific organ-failure support modalities like CRRT are used in these cases.

The predicted survival for cancer patients who develop secondary bacterial infection is decreased [11, 12], and it is only treated by the excessive use of antibiotics with the increased antibiotic resistance [13]. Over the past few decades, numerous experimental and clinical studies have investigated the efficacy of extracorporeal blood purification technologies in the treatment of specific indications like in sepsis and septic shock and rhabdomyolysis [14–16] (Fig. 1). Thus far, these therapies have failed to demonstrate an improvement in survival when evaluated in randomized trials. Examples may include inadequate timing for treatment initiation, different target molecules in various indications, and inadequate patient selection but on the same time hundreds of case reports reported positive effects of different hemoadsorbers.

For many years, the ICU admission of patients with cancer was questioned by some ICU physicians, but now even the therapies like ECMO have been demonstrated to offer favorable short- and long-term outcomes in cancer patients [17]. In this review article, our goal was to show the possibility of using different hemoadsorbers in specific indications in patients with cancer-related complications, their reported effectiveness in certain indications listed in the text, and the possibility of applying it to cancer patients not only as a last-stand therapy but as well as preventing the development of specific organ or multi-organ failure.

Rhabdomyolysis-Associated AKI

For many years the standard treatment of rhabdomyolysis-associated AKI was only of supportive nature. The release of myoglobin in the bloodstream, its damage of proximal tubule cells, and consequent development of AKI are facilitated by pro-oxidative effects, Tamm-Horsfall protein formation, direct tubular injury, and tubular cast formation [18]. Prolonged elevation in plasma myoglobin levels, therefore, continuously brings injury to the kidneys, thus making recovery of renal function becomes less likely. Creatinine kinase is released to the bloodstream following the muscle cell injury. It was often considered a more useful marker for diagnosis and severity assessment due to its delayed clearance, and it has not been associated with toxic effects [19]. In oncologic patients rhabdomyolysis develops either as a direct consequence of a cytostatic drug toxicity or as a paraneoplastic myositis [6, 7]. Muscle injury triggers an immune system response characterized by the migration of leukocytes into the damaged muscle tissue and results in the release of cytokines, prostaglandins, and free radicals. Consequently, these effects contribute to the development of AKI and often the provision of multi-organ support [20]. CytoSorb® (CytoSorbents Corporation, Monmouth Junction, NJ, USA) is a cytokine adsorber approved for infectious and non-infectious conditions and was used in patients with COVID-19 as well [21, 22]. The use of CytoSorb hemoadsorber in a study by Gräfe et al. [23] showed the potential for use in facilitating renal recovery in patients with severe rhabdomyolysis by removing myoglobin (p = 0.04; OR: 3.6). Study by Scharf et al. [16], showed similar effects of blood purification with CytoSorb during high-flux dialysis but they importantly noted that this effect might be obscured if the cause of rhabdomyolysis is not solved. Timely initiation of hemoadsorption therapy has shown promising benefits in managing certain critical conditions, including rhabdomyolysis by adsorption of myoglobin and other inflammatory mediators [24, 25]. Still, larger case series and a prospective randomized controlled trial are needed to confirm the effectiveness of this therapy.

Liver Failure

In cancer patients, liver failure can be a consequence from the chemotherapy toxicity and other supportive medications, cancer metastasis, Budd-Chiary syndrome, paraneoplastic syndrome, sepsis, or fungal liver disease [8]. In these patients liver failure rarely ends with cirrhosis and more often manifests as the acute exacerbation of existing chronic liver disease which has been officially referred to as acute-on-chronic liver failure (ACLF) [26]. ACLF can enhance the development of AKI [27] which can more adversely affect the prognosis of ACLF than can failure of any other single organ [28]. In

Table 1. Different causes and target molecules responsible for the development of specific cancer-related complications

Cause	Target molecule	Cancer-related complication
Cytostatic drug toxicity; paraneoplastic myositis	Myoglobin	Rhabdomyolysis-associated AKI
Chemotherapy toxicity; other supportive medications; cancer metastasis; Budd-Chiary syndrome; paraneoplastic syndrome; sepsis; fungal liver disease	Bilirubin; cytokines?	Liver failure
Every cause of AKI (i.e., ischemia or drug toxicity); sepsis	Cytokines; neutrophiles	Cytokine-mediated AKI
Immunotherapy	Cytokines	Cytokine release syndrome; hemophagocytic lymphohistiocytosis
Chemotherapy-related toxicity	Drug	Febrile neutropenia/infection; AKI; liver failure
Endotoxemia; bacterial gut-translocation	Endotoxins; LPS	Sepsis; septic shock
Secondary pathogen superinfection	Bacteria; viruses; fungi	Sepsis; septic shock
Cancer-chronic inflammation interaction	Pathogens	Immuno-exhaustion

AKI, acute kidney injury; LPS, lipopolysaccharides.

this two-faceted relationship between liver and kidneys we have limited therapeutic options when patients, such as those with oncological conditions, are not candidates for liver transplantation. To date, most studies have reported plasma exchange as a treatment of choice for ACLF, primarily due to its ability to eliminate proinflammatory cytokines [10]. Given that the development of liver failure is mediated by a systemic hyperinflammatory response, the therapeutic application of non-selective cytokine adsorbers is a rational and potentially beneficial strategy.

Although CytoSorb has been reported in most published studies, its use has been limited to a small cohort of patients with liver failure [29]. The only study which reported beneficial effects in patients with ACLF regarding detoxification by removal of bilirubin and decreasing inflammatory parameters (all $p < 0.02$) was by Haselwanter et al. [30]. An additional technique, double plasma molecular absorption system, which constitutes of two resins, a neutral macroporous resin (HA 330-II) and an anion-exchange resin (BS 330), was used in patients with liver failure. The studies reported efficient removal of macromolecules, medium-sized molecules and toxins with a disadvantage related to non-selective adsorption of the columns and consequently development of coagulation disorders and bleeding complications [31, 32]. While the rationale behind using hemoadsorption therapy to mitigate the hyperinflammatory response and thereby improve liver and subsequently kidney function is sound, larger randomized controlled trials are necessary to validate this hypothesis.

Cytokine-Mediated AKI

Every cause of AKI, in all patients as well as in cancer patients, like ischemia or drug toxicity is characterized by an inflammatory response where intrarenal immune cells starts actively secreting cytokines and chemokines which presumed role is to recruit leukocytes from the circulation to the injured part of the tissue [33]. The different leukocytes subtypes are summoned in a sequential manner where neutrophils, as the first line of defense, release granule contents at the local site in order to destroy invading pathogens, which is followed by activation of monocytes, which then differentiate into macrophages [34]. Cytokine-mediated inflammatory process plays a significant role in the pathogenesis in AKI [35]. The role of hemoadsorbers in removal of different target molecules through various parts of inflammatory cascade in patients with AKI was reported in numerous studies.

The usage of selective cytopheretic device (SCD, SeaStar Medical, Inc.) has been used primarily in pediatric patients with AKI [36, 37]. The device immunomodulates activated circulating leukocytes by low shear blood flow path which allows activated circulating neutrophils and monocytes to bind to the SCD's biocompatible membrane [38]. This

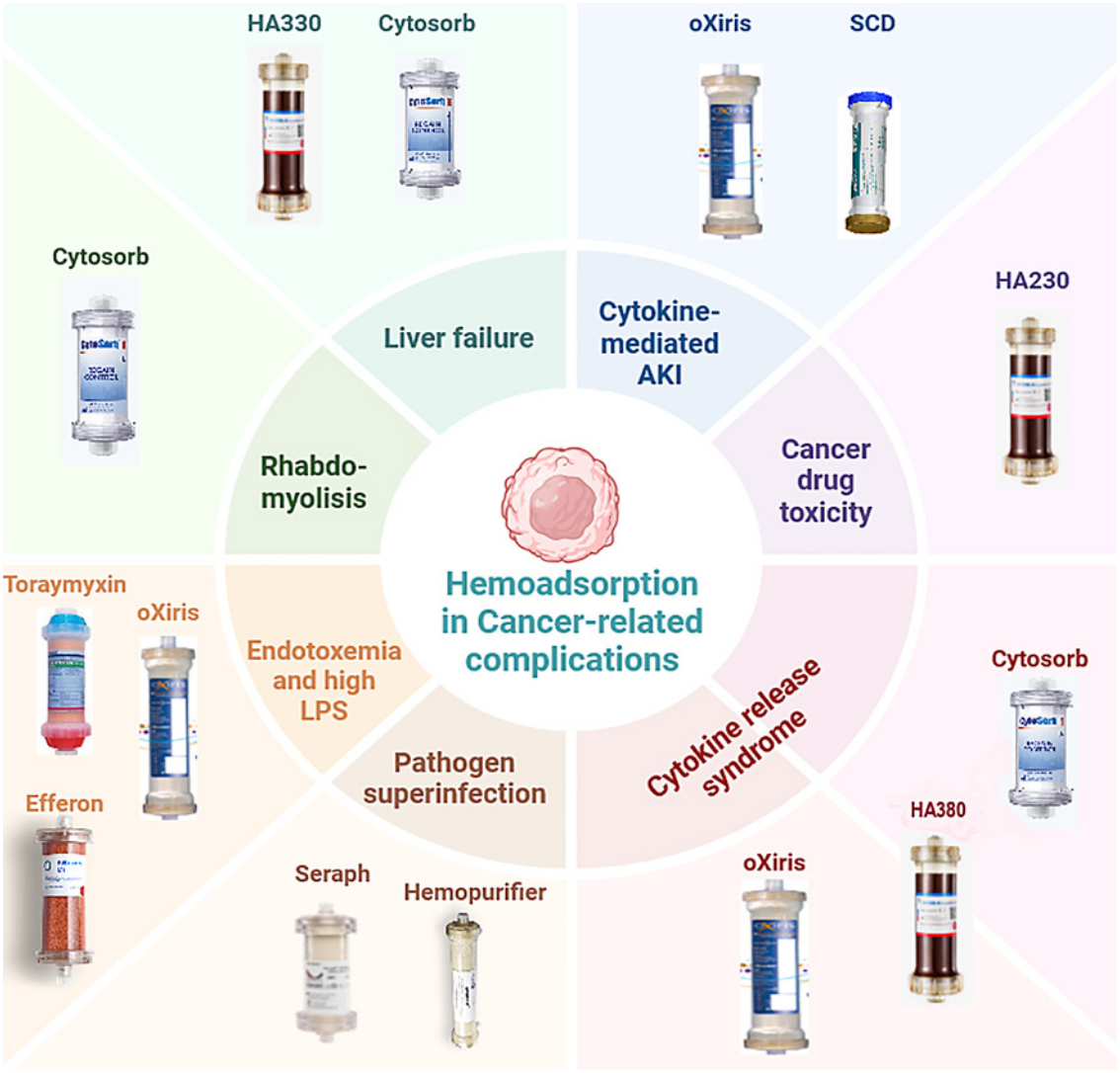

Fig. 1. Hemoadsorption in different cancer-related complications. AKI, acute kidney injury; SCD, selective cytopheretic device; LPS, lipopolysaccharide.

SCD-promoted selective sequestration results in a prolonged shift to a greater number of less inflammatory (reparative or patrolling) circulating monocytes while the bound neutrophils became apoptotic and are released back to the systemic circulation [38, 39]. Goldstein et al. [37] reported SCD treatments in twenty-two patients with AKI and multi-organ dysfunction receiving CRRT, after which 17 patients survived until ICU discharge or day 60 (77%; 95% CI, 55%–92%; p = 0.04). Fourteen of the 16 patients surviving ICU discharge reported a normal estimated glomerular filtration rate and no patient was dialysis dependent at 60 days. Although this study was performed in a small number of patients its results showed a potential benefit in patients with AKI characterized by a strong inflammatory response.

The oXiris hemofilter has been primarily utilized in patients with AKI for the removal of high levels of cytokines. The surface of the oXiris filter is coated with both polyethyleneimine and heparin where the negative charges of the AN69 membrane can effectively adsorb cytokines [40]. Turani et al. [41] reported, in sepsis/septic shock patients with AKI, treated with CRRT and oXiris, the improvement of the main cardiorenal and respiratory parameters as well as a decrease of the noradrenaline dosage, cytokines, procalcitonin, endotoxins and the improvement of the SOFA score.

Cytokine Release Syndrome

Based on the understanding of cellular immune regulation, new methods for cancer treatment have emerged. In addition to monoclonal antibodies and antibody-drug conjugates against tumor cells, some novel immunotherapeutic approaches such as immunologic checkpoint blocking or CAR-T-cell therapies have been developed. Although CAR-T-cell therapy showed more than promising results in hemato-oncological patients the results in patients with solid tumors were not that promising [42]. Furthermore, it has been reported that administration of CAR-T-cell therapy can lead to life-threatening adverse events including early onset events such as cytokine release syndrome (CRS), neurotoxicity, and late toxicities such as hemophagocytic lymphohistiocytosis [43]. CRS is caused by the rapid immune activation induced by CAR-Ts, leading to a considerable elevation in the levels of inflammatory cytokines. It is the most common acute toxicity associated with CAR-T therapy. CRS initially manifests with fever and hypotension but may progress to life-threatening vasodilatory shock, capillary leak, hypoxia, and end-organ dysfunction [44]. The Jafron HA380 cartridge (Jafron Medical, Zhuhai, China) has been designed as a non-selective adsorption device for clinical conditions characterized by elevated cytokine levels [45] and its use, the same as for CytoSorb and Oxiris, should be initiated in cancer patients with CRS even before the development of end-organ dysfunction with the same rationale as in other acute inflammatory conditions like sepsis [41, 46, 47]. This therapy has been explored in cancer patients with severe or refractory CRS following CAR-T therapy and provided some promising results regarding the mitigation of inflammation and improvement of hemodynamics [48, 49].

Drug Toxicity

Chemotherapy is still a basic treatment for most of cancer types but most of these drugs have reported side effects which even in therapeutic doses can have unfavorable effects to non-malignant dividing cells and, therefore, causing organ damage [50]. Chemotherapy-associated toxicities are often manifested as severe neutropenia, febrile neutropenia, and infection. In most cases, it is treated with colony-stimulating factor, antibiotics use or with the reductions in chemotherapy relative dose intensity. Some reported more than 60% of patients with stage IV solid tumors who underwent reductions in chemotherapy relative dose intensity [51]. High-dose methotrexate is still playing a significant role in the treatment of different types of malignancies in children and adults, including acute lymphoblastic leukemia, non-Hodgkin lymphoma, osteosarcoma, and others [52]. However, high-dose methotrexate can cause various toxic effects to liver, kidneys, and brain. It was previously reported the use of different extracorporeal methods like plasma exchange, hemodiafiltration and hemoperfusion but without significant proofs of methotrexate elimination. The study by Sazonov et al. [53] reported an effective removal of blood methotrexate level by 85.27% and the reduction of its toxicity due to decreased clearance in a pediatric patient with acute lymphoblastic leukemia after high-dose methotrexate. The use of hemoadsorption for drug removal is highly dependent on the drug´s characteristics such as molecular weight, protein binding, and hydrophobicity, which determine how effectively it can be adsorbed by devices, and still remains uncertain due to limited evidence, with only one study currently available. The intended use of hemoadsorption in this context is likely not to remove the chemotherapeutic agent itself but rather to mitigate the downstream inflammatory or metabolic consequences induced by the treatment [54, 55].

Endotoxemia and Sepsis

Cancer patients during chemotherapy often develop febrile neutropenia which in most cases is not confirmed with blood cultures. Infection can be caused from bacterial translocation in which intestinal bacteria and endotoxins pass through the intestinal wall, enter the blood circulation, and spread to other sites of the body, such as lymph nodes, spleen, liver, and kidney [9]. This risk is further increased with surgery, radiation, and chemotherapy where mucositis is worsening.

Translocation of bacterial products or endotoxins from the gut is a dominant source of endotoxemia, and it has been reported that 70% of patients with septic shock and high endotoxin activity have negative blood cultures [56]. Bacterial endotoxins, represented by lipopolysaccharides (LPSs), which constitute up to 75% of the outer membrane of gram-negative bacteria, are primary triggers for the pathogenesis of sepsis [57].

Damage-associated molecular patterns further promote proinflammatory dysregulation through increased synthesis release of cytokines, chemokines, coagulation factors, and complement [58]. In severe endotoxic shock, particularly for gram-negative sustained sepsis with severe bacteremia, endotoxin neutralization by blood purification therapy might prevent or reduce the physiological (mainly hemodynamic) derangement typically observed in these patients. This therapeutic approach can be provided in combination with CRRT and with other highly adsorptive cartridges that

target removing pro- and anti-inflammatory cytokines [59]. The most prevalent cartridge used for the removal of endotoxin is the polymyxin B hemoadsorber (PMX). The PMX device functions through the immobilization of polymyxin B antibiotic inside the columns of a cartridge which adsorbs endotoxins without the systemic toxicity of the drug itself. It is mostly used during the early phase of a septic shock caused by Gram-negative bacteria [60]. The EUPHAS trial found a significant improvement in survival (adjusted HR, 0.36; 95% CI, 0.16–0.80) with early PMX use in a targeted population with severe sepsis and/or septic shock from intra-abdominal gram-negative infections, whereas the Euphrates trial failed to find an improvement in survival after PMX use [56, 61]. The use of PMX and a recently reported use of Efferon LPS hemoperfusion device could be especially appliable in cancer patients with neutropenia, the development of sepsis and negative blood cultures where presumably gut-translocated endotoxins and LPSs causes hyperinflammatory immune response [62]. When considering removal of endotoxins with hemoadsorption technique we should take into account the design of the oXiris hemofilter which uses the negative charges of the AN69 membrane to adsorb cytokines while the positively charged polyethyleneimine captures endotoxins [40]. In vitro studies have shown that oXiris simultaneously removes endotoxins comparably to PMX and cytokines comparably to CytoSorb [59].

Pathogen Superinfection

During cancer treatment the development of bacterial infection is one of the most frequent complications [63] and although survival of cancer patients is, in recent years, increasing, bacterial infections remain a significant cause of mortality mostly as a complication of chemotherapy, radiotherapy, and immunosuppressive drugs [11, 12]. Bacterial infections are eightfold higher prevalent in patients with blood cancers compared to patients with solid cancers mostly due to prolonged neutropenia as a consequence of treatment and in patients failing to respond to cancer therapy [64, 65]. The obstruction caused by tumor can redispose patients to infection [66]. The excessive antibiotic use in cancer patients with prolonged neutropenia and frequent re-infections with the same or different bacteria is one of the mains reasons of antibiotic resistance and bacterial infection-related mortality in these patients [13]. A new approach in hemoadsorption recently started with a shift in focus from non-selective cytokine binding devices to pathogen-binding cartridges. The Seraph-100® Microbind®Affinity Blood Filter (Seraph-100®; ExThera Medical Corporation, Martinez, CA, USA) is an extracorporeal hemoperfusion device with a broad-spectrum sorbent capable of binding bacteria, viruses, and fungi in the blood, including SARS-CoV-2 [67, 68]. The technology is based on heparin-bonded polyethylene beads that bind to, and remove, microorganisms similar to the interaction with heparan sulfate within the endothelial glycocalyx [67]. In the first in-human safety study on Seraph-100 device in bacteremic hemodialysis patients, no adverse events occurred in patients with bacteremia at the time of treatment, and a significant increase in time to positivity of the blood cultures was demonstrated, reflecting a reduction in pathogen load [68]. The results from a study using a sequential extracorporeal blood purification strategy, the combination of Seraph and non-selective hemoadsorbers in ICU patients with COVID-19 and confirmed sepsis showed a strong association with prolonged survival in comparison to non-selective hemoadsorption (22.4 [95% CI 19.8, 24.9] vs. 18.7 [95% CI 16.1, 21.3] days; $p < 0.001$) [69]. This rationale of sequential hemoadsorption can also be administered in cancer patients either with bacterial or fungal superinfection.

In immunocompromised cancer patients with sepsis and patients with hematopoietic cell transplantation, viral reactivation of CMV, EBV, adenovirus, and other viruses can lead to viral disease or active infection leading to significantly increased risks of graft rejection, pneumonia, ARDS, hepatitis, encephalitis, malignancy and mortality [70, 71]. The Hemopurifier® (Aethlon Medical, San Diego, CA, USA) combines plasmapheresis and an adsorption mechanism to remove viruses from the blood. The adsorption agent is a lectin protein with a strong affinity for the ubiquitous glycoproteins present on the surface of different enveloped viruses such as the coronaviruses, hepatitis C, and the filoviruses [72, 73]. Minimizing the development of systemic or organ specified complications, and reduction of secondary bacterial or fungal infections is of particular importance in this group. Adding an extracorporeal blood purification therapy in critically ill ICU patients with immunosuppression and high viral load may have a beneficial effect and can be considered as a possible alternative therapeutic strategy in these patients.

Conclusions

Currently, multiple forms of extracorporeal blood purification are available that may have benefit in patients with cancer-related complications. Various hemoadsorbers with specific properties for subtractive medical therapy have been used based on the target molecules and the

patient syndrome. Despite a strong rationale for extracorporeal blood purification many physicians are still reluctant introducing hemoadsorption as a recommended routine due to still insufficient evidence, mostly as a result of inadequate numbers of published randomized controlled trials. Nevertheless, the application of hemoadsorption should be the same for cancer-related complications as well as is it for other patients because in most cases we aim to remove the same target molecules.

Conflict of Interest Statement

The authors declare there is no conflict of interest related to the present manuscript and provide the following disclosures: Vedran Premuzic has received speaker and/or consulting honoraria from Fresenius Medical Care, Baxter Healthcare Corp, and Cytosorbents, all unrelated to this manuscript. Lui Forni discloses consulting fees paid by bioMérieux, unrelated to this manuscript.

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Author Contributions

V.P. is the corresponding author and has contributed to the preparation of the manuscript (writing, editing of text, and approval of the final manuscript). L.G.F. has contributed to writing, editing of text, and approval of the final manuscript. The authors read and approved the final manuscript.

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