DOI: 10.20514/2226-6704-2021-12-2-104-112 УДК 616.61.616.06;616-006.

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ХРОНИЧЕСКАЯ БОЛЕЗНЬ ПОЧЕК И ЗЛОКАЧЕСТВЕННЫЕ НОВООБРАЗОВАНИЯ: СОВРЕМЕННОЕ СОСТОЯНИЕ ПРОБЛЕМЫ

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Chronic Kidney Disease and Malignant Neoplasms: The Current State of the Problem

Резюме

Хроническая болезнь почек является фактором риска заболевания других органов. Больные с патологией почек имеют повышенный риск развития и смерти от сердечно-сосудистых заболеваний, кроме того, есть также свидетельства того, что риск рака и смертность от рака могут быть увеличены у людей с хронической болезнью почек. Хроническая болезнь почек и злокачественные новообразования взаимосвязаны в обоих направлениях: рак может вызывать прямое поражение почечной ткани или косвенное через побочные эффекты лечения онкологического процесса. В свою очередь хроническая болезнь почек, наоборот, может быть фактором риска развития злокачественных новообразований. Кроме того, оба патологических процесса могут иметь общие факторы риска. Хроническая болезнь почек может возникнуть в результате применения химиотерапевтических средств. Многие из существующих и недавно разработанных химиотерапевтических агентов против рака нефротоксичны и могут способствовать дисфункции почек, которая часто проявляется на терминальных стадиях рака. На сегодняшний день терапевтические вмешательства в борьбе с прогрессирующим ростом онкологических заболеваний может ускорить развитие хронической болезни почек. В статье приводятся данные о взаимовлиянии хронической болезни почек и развития злокачественных новообразований. Рассмотрены нефрологические аспекты клинической картины онкологических заболеваний. Обсуждаются механизмы негативного влияния на почечную ткань противоопухолевых препаратов — цисплатина, ифосфамида, метотрексата и циклофосфамида. Учитывая связь между заболеванием почек и развитием, а также и лечением рака, в обзорной статье подчеркивается важность междисциплинарного сотрудничества между онкологами и нефрологами для прогнозирования и предотвращения нефротоксичных эффектов проводимой противоопухолевой химиотерапии, а по мере внедрения новых методов лечения злокачественных новообразований требуется надлежащая диагностика и лечение возникающих в ходе терапии новых почечных токсических эффектов.

Ключевые слова: *хроническая болезнь почек, злокачественные новообразования, нефротоксичность, канцерогенное действие лекарств, цисплатин, ифосфамид, метотрексат, циклофосфамид*

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Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 13.05.2021 г.

Принята к публикации 03.11.2021 г.

Для цитирования: Муркамилов И.Т., Сабиров И.С., Фомин В.В. и др. ХРОНИЧЕСКАЯ БОЛЕЗНЬ ПОЧЕК И ЗЛОКАЧЕСТВЕННЫЕ НОВООБРАЗОВАНИЯ: СОВРЕМЕННОЕ СОСТОЯНИЕ ПРОБЛЕМЫ. Архивъ внутренней медицины. 2022; 12(2): 104-112. DOI: 10.20514/2226-6704-2021-12-2-104-112

Abstract

Chronic kidney disease is a risk factor for other organ disease. People with kidney disease have an increased risk of developing and dying from cardiovascular disease, and there is also evidence that the risk of cancer and cancer mortality may be increased in people with chronic kidney disease. Chronic kidney disease and malignant neoplasms are interconnected in both directions: cancer can cause damage to the kidney tissue directly or indirectly through the side effects of cancer treatment. In turn, chronic kidney disease, on the contrary, can be a risk factor for the development of malignant neoplasms. In addition, both pathological processes can share common risk factors. Chronic kidney disease can result from the use of chemotherapy drugs. Many of the existing and recently developed cancer chemotherapeutic agents are nephrotoxic and can contribute to renal dysfunction, which often manifests itself in terminal cancer. To date, therapeutic interventions to combat the progressive growth of cancer can accelerate the progression of chronic kidney disease. The article provides data on the interaction of chronic kidney disease and the development of malignant neoplasms. The nephrological aspects of the clinical picture of oncological diseases are considered. The mechanisms of the negative effect on the renal tissue of anticancer drugs — cisplatin, ifosfamide, methotrexate and cyclophosphamide — are discussed. Given the link between kidney disease and the development and treatment of cancer, the review article highlights the importance of interdisciplinary collaboration between oncologists and nephrologists to predict and prevent nephrotoxic effects of cancer chemotherapy, and as new treatments for malignant neoplasms are introduced, proper diagnosis and treatment of emerging malignancies is required. new renal toxic effects.

Key words: *chronic kidney disease, malignant neoplasms, nephrotoxicity, carcinogenic effect of drugs, cisplatin, ifosfamide, methotrexate and cyclophosphamide*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 13.05.2021

Accepted for publication on 03.11.2021

For citation: Murkamilov I.T., Sabirov I.S., Fomin V.V. et al. Chronic Kidney Disease and Malignant Neoplasms: The Current State of the Problem. The Russian Archives of Internal Medicine. 2022; 12(2): 104-112. DOI: 10.20514/2226-6704-2021-12-2-104-112

AKI — acute kidney injury, CF — cyclophosphamide, CKD — chronic kidney disease, GFR — glomerular filtration rate, GLN — glomerulonephritis, HD — hemodialysis, MNs — malignant neoplasms, NS — nephrotic syndrome, PS — paraneoplastic syndrome, WHO — World Health Organization

Introduction

Risk factors of malignancies, as well as of other chronic non-communicable diseases, including chronic kidney disease (CKD), are largely similar. The incidence of malignant neoplasms (MNs) has undoubtedly increased progressively everywhere in recent years. The increasing incidence of malignant neoplasms in the general population is due to a higher life expectancy, urbanization, new carcinogenic factors, hereditary burden, improved diagnosis of cancer, etc. [1]. According to the World Health Organization (WHO), cancer is the second leading cause of death in the world [2]. In 2018, 9.6 million people died from neoplasms [2]. Cancer causes almost one in six deaths worldwide [2]. N.F. Bakalets et al. (2016) reported that more than 10 million new cases of neoplasms are recorded annually in the world, and this number is growing every year [3]. According to the Republican Medical Information Center in Kyrgyzstan, malignant neoplasms rank second among the causes of death. In 2018 alone, 4.1 thousand deaths from neoplasms were registered, which is 12.6% of the total number of deaths. Among those who died from oncological diseases, mortality among people of working age amounted to 1,800, or 43.3% of the total number of deaths from this cause, and among elderly groups — 2,300 deaths, or 54.7%. It should also be noted that MNs accounted for 10.1% of the causes of primary disability.

According to the literature, MNs increase the risk of kidney diseases, and the presence of MNs has a negative impact on the general prognosis [4]. At the same time, patients with CKD at the stage of renal failure have a higher risk of developing malignant neoplasms of different localizations [5]. Therefore, CKD is an independent predictor of the development of MNs. In addition, individuals with kidney tumors have a higher risk of

developing and progressing CKD associated with therapeutic and diagnostic measures for kidney cancer [4].

Colon and rectal cancer is the third most common cancer and the second leading cause of cancer-related deaths worldwide [6]. The high risk of developing colorectal cancer in patients with CKD was shown in a meta-analysis conducted by Komaki Y. et al. in 2018 [7]. Survival rates of patients with CKD and colon and rectal neoplasms were significantly lower [7].

A population-based cohort study revealed that the relative risk of developing cancer in men with glomerular filtration rate (GFR) of less than 55 mL/min is significantly higher, while the risk of developing cancer increases by 29% for every 10 mL of GFR decrease. The incidence of non-Hodgkin's lymphoma, Kaposi's sarcoma, and lip, colon, and thyroid cancer was significantly higher in patients with CKD [8]. It should be said that the risk of MNs is also high in individuals on long-term hemodialysis (HD) [9]. In this regard, some researchers recommend regular screening for MNs in patients on long-term HD for more than 3 years, which can increase their life expectancy [9]. Meanwhile, other researchers believe that, despite the increased risk of developing malignant neoplasms in patients receiving chronic HD, routine screening for all individuals is not recommended [9]. Regular screening should be individualized according to the patient's life expectancy and the possibility of kidney transplantation in the future [8,9,10]. It should be noted that the incidence and nature of MNs in individuals with CKD may vary in different geographical areas. A meta-analysis performed by Leeaphorn N. et al. (2014) demonstrated that the prevalence of MNs in patients with membranous glomerulonephritis (GLN) in most residents reaches up to 10% [11]. It is significant that this meta-analysis pooled the results of six studies, with a total of 785 patients; the average age of participants with membranous GLN and cancer was 67±7 years, and in 20±6.8% of cases, the diagnosis of cancer preceded the diagnosis of membranous GLN [11]. Lung and prostate cancer account for the vast majority of tumors associated with membranous GLN. Hematological malignancies should also be considered one of the potential types of cancer associated with membranous GLN [11].

According to Heaf J.G. et al. (2019), hypertensive nephropathy is associated with an increased risk of skin and kidney cancer [12]. The risk of developing MNs in cases of CKD is thought to be associated with proteinuria and GFR value. Later, a population-based study performed by Ahn S.Y. et al. (2020) demonstrated the relationship between proteinuria and an increased risk of developing neoplasms [13]. Various types of MNs were associated with GLN, or were identified during the diagnosis of GLN [14]. Ryu J. et al. (2019) analyzed the clinical and laboratory data of 1,155 patients with GLN after nephrobiopsy [15]. The age of participants was 49,7±17,3 years. Individuals with IgA nephropathy accounted for 37.9% of those examined, while patients with membranous GLN accounted for 13.5% [15]. The incidence of MNs was three times higher in patients aged 50+ with GLN compared with the general population [15]. Amyloidosis was the most common type of GLN associated with MNs (20.7%) [15]. Compared with other types of GLN, MNs were observed in patients with amyloidosis almost 28 times more often than in the general population [15].

The development of CKD in patients with malignant neoplasms may be due to the risk factors and the effect of treatment that potentiates oncogenesis. In 2014, I.B. Kolina and I.N. Bobkova published an article on the problems of kidney damage in MNs [5]. The authors identify the following types of nephropathies in cases of MNs depending on the mechanism of development [5]:

- Lesions caused by the mechanical impact of the tumor.
- Lesions caused by tumor management.
- Paraneoplastic nephropathies.
- Lesions caused by metabolic factors.

Long-term hormonal therapy is accompanied by changes in the metabolism of lipids, carbohydrates and purines, leading to an increased risk of development and progression of atherosclerosis [16]. Also, several oncological agents used in the management of malignant neoplasms can induce vascular damage, even if there are no other risk factors [16]. In particular, cisplatin, paclitaxel, L-asparaginase, methotrexate, 5-fluorouracil cause endothelial dysfunction and can lead to kidney diseases [16]. Damage to renal glomeruli in cases of MNs is rare and morphologically heterogeneous [17, 18]. Sudden deterioration of kidney function and tumor lysis syndrome were described in detail in the published work by I.B. Kolina and I.N. Bobkova [5].

Paraneoplastic Syndromes

Paraneoplastic syndrome (PS) refers to non-specific syndromes of malignant growth. According to present-day information, PS includes various pathological manifestations due to the indirect influence of the tumor process on metabolism, immunity, and functional activity of different organs [18]. The term "paraneoplastic syndrome" has been used in the medical vocabulary since 1948. In 2010, in the 3rd issue of the "Clinical Nephrology" journal, an editorial was published under the title "E.M. Tareyev and the doctrine of nephritis (for the 115th anniversary)" [19]. It describes a variety of clinical and morphological variants of kidney damage in connection with paraneoplastic and paratuberculous syndromes [19]. In the case of PS with the same malignant tumor (for example, nephrocarcinoma or lymphogranulomatosis), one patient may develop GLN (more often membranous GLN, although other morphological variants of GLN are possible), and another may develop

amyloidosis [19]. It is difficult to predict the variant of kidney damage since, in this situation, as in the case of "cold", drug-induced, and finally infectious factors, nephritis is a manifestation of individual hypersensitivity [19]. The emphasis made by E.M. Tareev in this argument is very important to understand his view on the theoretical concepts of the pathogenesis of nephritis and especially on approaches to the classification of kidney diseases [19].

In 1922, Galloway introduced the concept of paraneoplastic glomerulopathy [20]. However, the first original study that established the relationship between cancer and nephrotic syndrome (NS) was published in 1966 by Lee J.C. et al [21]. In the Russian-language literature, the interest in PS was primarily aroused by the works of E.M. Tareev and his scholarly tradition, which, for the first time, described nonspecific reactions in patients with malignant neoplasms of different localizations [22–24].

The published work by L.I. Anikonova et al. (2016), lists criteria for PS-related glomerulopathy: 1) chronological relationship between the diagnosis of glomerular syndrome and the tumor; 2) parallel evolution of the tumor and of the syndrome of achieved specific cytotoxic therapy; 3) existence of a pathogenetic relationship between glomerulopathy and the tumor [25]. If we consider certain types of neoplasms, then the relationship between NS and chronic lymphocytic leukemia was established as early as 1957 [30]. Researchers at I.I. Mechnikov North-West State Medical University (St. Petersburg) described a clinical case where a patient developed severe NS with acute kidney injury (AKI) six years after the diagnosis of chronic lymphocytic leukemia, and the results of nephrobiopsy revealed focal segmental glomerulosclerosis and acute tubular lesions [25]. According to the researchers, in up to 50% of cases in clinical practice, the development of paraneoplastic NS precedes tumor manifestations, often contributing to its detection; parallelism between tumor relapses and renal syndrome is not always observed [25].

Excessive production of growth factors, pro-inflammatory cytokines, and various antigens in cases of MNs is accompanied by kidney damage [5]. Tumor cells can produce cytokines and lymphokines that cause podocyte dysfunction, which is accompanied by impaired permeability of the glomerular filter. Glomerular injury can be caused by direct exposure to cryoglobulin-producing tumor cells followed by complement activation via an alternative pathway. There is formation of intracapillary thrombi, which consist of cryoglobulin precipitates. There is also massive infiltration of glomeruli by macrophages and monocytes, which contributes to kidney damage in PS [26]. In addition, the independent role of tumor tissue antigens in the development of certain morphological types of glomerulopathies is currently being actively studied [26]. Hyperproduction of antibodies under intensive tumor growth leads to the formation of immune complexes, which enter kidneys from the systemic circulation and accumulate in subepithelial space [26]. Renal manifestations of oncological disease progress and are clinically manifested by hematuria, proteinuria, hypo- and dysproteinemia, hyperfibrinogenemia [5, 22, 23]. In their work, Zafar-Mohtashami A. et al. (2020) described the development of paraneoplastic NS in a 65-year-old patient with carcinoma of unknown primary site [27]. According to the researchers, NS was completely resolved with chemotherapy. In another observation, the development of nephrotic level proteinuria was observed in a 55-year-old woman with ovarian cancer. As a result of surgical removal of tumor and glucocorticoid therapy, NS remission and preserved kidney function were observed [28].

The most common type of paraneoplastic nephropathy in malignant neoplasms is membranous GLN [24]. Paraneoplastic membranous GLN is often resistant to standard immunosuppressive regimens, although sometimes an initial decrease in proteinuria and other signs of NS can be observed [18]. Patients with MN may develop mesangiocapillary GLN and minimal change disease, although these types of kidney damage are more typical for lymphoproliferative diseases [23]. Mesangiocapillary GLN was described in patients with Wilms' tumor, malignant melanoma, and also as part of PS in lung cancer [23]. Minimal change disease has been described in cases of different carcinomas. Combinations of minimal change nephropathy with rectal cancer are known; in this context, hyperproduction of vascular endothelial growth factor was found [23]. Minimal change disease can develop in cases of pleural mesothelioma [23]. There are reports of completely resolved NS after surgical removal of tumor [28]. However, the small number of observations does not allow to make a conclusion about a causal relationship between MN and this type of kidney damage [24].

Liu X. et al. observed a 59-year-old man with lung adenocarcinoma and membranous GLN that was manifested by the swelling of lower limbs, hypoproteinemia, and proteinuria [29]. It is noteworthy that therapy with an epidermal growth factor receptor tyrosine kinase inhibitor (erlotinib) led to the stable remission of paraneoplastic membranous GLN associated with lung adenocarcinoma [29]. The development of membranous GLN in cases of lung cancer is associated with a mutation of the gene that encodes EGFR (epidermal growth factor receptor). It should be noted that according to world statistics, lung cancer remains the most common type of cancer (1.6 million new cases annually). Approximately 70–80% of membranous GLN is due to primary kidney diseases; secondary forms develop due to autoimmune diseases, infections, drug exposure, or MNs [30]. The aspects of GLN associated with MNs are being actively studied [30]. Higashihara T. et al. (2020) report on a case of NS in a patient with squamous cell lung cancer and the effectiveness of chemoradiotherapy in relation to proteinuria

and tumor growth [31]. The patient had a morphological pattern of proliferative GLN with deposits of monoclonal immunoglobulin λ-chain. In the above study, the authors note that literature describes more than 130 patients with renal damage associated with lymphocytic leukemia who underwent nephrobiopsy due to NS or unclear renal dysfunction [31].

Other potential causes of renal dysfunction in patients with MNs are tumor lysis syndrome, chemotherapy toxicity, ureteral obstruction by enlarged lymph nodes [5]. Among chemotherapy agents, cisplatin (10–80%), ifosfamide (1.4–30%), methotrexate (1.8–12%) and carboplatin (0–25%) have the greatest nephrotoxic effect [32]. Cisplatin is one of the most widely used agents in the management of MNs (tumors of ovaries, testicles, head, neck) and is known to be one of the most nephrotoxic drugs. Cisplatin causes severe tubular damage, predominantly in proximal tubules, electrolyte imbalance, AKI, and thrombotic microangiopathy [33]. In connection with long-term treatment, arterial hypotension as a result of hyponatremia and decreased circulating blood volume are often observed. This may create a premorbid background for the development of AKI or the progression of CKD, especially in elderly patients. Nephrotoxicity is more dependent on the dose of cisplatin used. A single injection of the medication at a dose of less than 50 mg/m^2 rarely causes AKI [34]. The role of cisplatin in the development of CKD was established in a number of experimental studies where the molecular and cellular mechanisms of cisplatin nephrotoxicity were summarized [35]. Cisplatin-induced AKI is based on increased expression of biomarkers of tubular injury, increased oxidative stress, inflammation, apoptosis, and necrosis of tubular epithelium [35]. All patients treated with cisplatin have magnesium deficiency [34]. There are reports that the initial magnesium deficiency in the blood of MN patients increases the risks of AKI associated with cisplatin, and the correction of magnesium-deficient conditions, or the administration of magnesium to MN patients during their treatment with cisplatin significantly reduces its nephrotoxicity [36]. In literature, the role of oxidative stress is discussed, which is caused by mitochondrial dysfunction and intracellular accumulation of reactive oxygen intermediates, which is an important feature of cisplatin-induced AKI [37]. In proximal tubules, after receptor-mediated endocytosis, cisplatin is hydrolyzed into a positively charged molecule [38]. Also, Klotho protein is thought to play a protective role in the development of AKI in patients with cisplatin-induced malignant neoplasms [39]. According to researchers, approximately 30–60% of children treated with cisplatin develop severe tubular and/or glomerular damage [32]. In adults, high doses of cisplatin can cause significant cardio-, nephro- and cerebrotoxic effect. Neurological manifestations of decreased magnesium level in blood serum can include headaches, dizziness, fainting, feeling of shortness of breath, hyperacusis, increased fatigue, poor tolerance to bright light, seeing dark spots in one's vision, crawling sensation, impaired memory and concentration, hyperactivity, fear, depression, irritability, sleep disturbances. In some cases, cardiac manifestations of hypomagnesemia (severe cardiac arrhythmias, arterial hypotension) can induce kidney dysfunction [40].

Another medication with a negative effect on proximal tubules is ifosfamide, which has structure and action similar to cyclophosphamide (CF). Ifosfamide induces damage to proximal tubules by metabolites and leads to energy depletion of tubular cells. The above study noted that ifosfamide can damage the distal tubules, leading to nephrogenic diabetes [34]. Some researchers highlight the delayed nephrotoxic effect of ifosfamide in the form of decreased GFR as a result of glomerular damage, hypophosphatemia, hypokalemia, hypomagnesemia, hyperaminoaciduria, glucosuria, and hyperphosphaturia due to the tubular toxicity of this agent [40]. Young age and a cumulative dose of the drug of 45 g/m^2 are the main risk factors for the development of nephrotoxicity; the toxic cumulative dose of this drug is 60–72 g/m^2 [40]. In 2004, Rogowska E. and Woźniak W. described a case of Fanconi syndrome in a 13-year-old patient with skin cancer treated with high doses of ifosfamide [41]. One year later, another case was described when a 58-year-old woman with MN, after five cycles of chemotherapy with ifosfamide, developed tubular proteinuria, glycosuria, and microhematuria [42]. Three months after another cycle of treatment with ifosfamide (treatment cycle 6), the patient had general weakness and nocturia, and HD sessions were started due to azotemia [42]. Another observation described a case of Fanconi syndrome 17 months after the administration of ifosfamide for the management of Burkitt lymphoma in a two-year-old child [43]. It is worth noting that about 30% of children treated with ifosfamide have tubular damage [32]. In 18–28% of cases, AKI and CKD develop during the administration of ifosfamide [34]. The risk of ifosfamide nephrotoxicity increases significantly with age and in the presence of comorbid pathologies. Considering that the course of ifosfamide nephrotoxicity is often asymptomatic, careful laboratory monitoring is necessary, with a focus on renal tubular function.

In the mid-20th century, American pediatrician Farber S. (09/30/1903–03/30/1973) founded the Pediatric Cancer Research Foundation and investigated the effectiveness of various medications [44]. Farber's most famous achievement was the agent named "methotrexate", which was synthesized at his request by the brilliant chemist Yellapragada Subba Row (01/12/1895–08/08/1948). This medication is still one of the key anticancer chemotherapy drugs. Methotrexate is a cytotoxic drug from the group of antimetabolites, folic acid antagonists. Methotrexate has significant

Table 1. *Anticancer drugs associated with acute kidney injury [50]*

Medication	Mechanism of action	Renal histopathologic features	Clinical nephrotoxic effects
Cisplatin	Cross-linking and interference with DNA replication	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi syndrome, NDI, sodium and magnesium wasting
Ifosfamide	Nitrogen mustard alkylating agent; inhibition of DNA synthesis through DNA strand-breaking effects	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi syndrome, NDI
Pemetrexed	Antifolate agent; inhibition of dihydrofolate reductase, thymidylate synthase, and glycinamide ribonucleotide formyltransferase	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi syndrome, NDI
Methotrexate	Antifolate agent; inhibition of dihydrofolate reductase	Crystalline nephropathy and acute tubular injury	Acute kidney injury
Pamidronate	Pyrophosphate analogue; associated with moderate FPPS inhibition	Focal segmental glomerulosclerosis, acute tubular injury	Nephrotic syndrome, acute kidney injury
Zoledronic acid	Pyrophosphate analogue; associated with potent FPPS inhibition	Acute tubular injury and acute tubular necrosis	Acute kidney injury

immunosuppressive effect, even at relatively low doses that have no noticeable hematological toxicity. As a result, methotrexate is widely used in comparison with other cytostatics. Methotrexate is more active against rapidly growing cells and is excreted by the kidneys [34]. High doses of methotrexate under acidic urine reaction conditions lead to the precipitation of metabolite crystals inside the tubules [34]. Approximately 47% of patients show signs of nephrotoxicity during the administration of high doses of this drug; they are accompanied by decreased GFR [45]. Adequate hydration and urine alkalinization are standard parts of the program when using high doses of methotrexate [34]. Methotrexate often causes electrolyte disturbances, particularly hypokalemic acidosis and hypocalciuria [34]. Also, methotrexate tends to accumulate in tissues, causing toxic liver damage and myelodepression. Previous studies demonstrated the independent role of high doses of methotrexate in the development of CKD in cases of MN in the pediatric population [46]. High doses of methotrexate lead to a persistent decrease in GFR and may cause proteinuria several years after the end of treatment [46]. Factors that increase the risk of nephrotoxicity are high doses of methotrexate, reduced GFR, elderly age, male gender, and polypharmacotherapy (antibiotics and proton pump inhibitors) [47].

Cyclophosphamide (CF) has a wide spectrum of antitumor activity. CF has significant immunosuppressive effect with predominant inhibition of Blymphocytes. Antitumor activity is achieved directly in cells of the malignant tumor, where CP is biotransformed under the action of phosphatases, forming an active metabolite with an alkylating effect. E.I. Dorokhina et al. (2016) report that CF has a direct damaging effect on the urinary system and can cause hemorrhagic cystitis [40]. The nephrological risk of CF is that this drug causes hyponatremia, which manifests within one hour after administration and disappears in two days. Hyponatremia is caused by impaired excretion of water by the kidneys. Hyponatremia is probably associated with the effect of CF on distal tubules. Hyponatremia usually develops in acute form and resolves after discontinuation of the medication. Trisenox (arsenic trioxide) is one of the main cytotoxic agents used in the management of cancer. Nephrotoxic effects are manifested in the form of tubulointerstitial nephritis and rhabdomyolysis [48]. Besides anticancer agents, nephrotoxic antibiotics, antiviral and antifungal drugs used to manage infectious complications can also induce changes in the kidneys [34, 40, 48, 49].

Basic variants of nephropathies caused by anticancer agents are presented in tables according to the KDIGO conference (2018) on onconephrology dedicated to the study of kidney damage in cases of malignant neoplasms of solid organs [50].

Therefore, it can be noted that there are different mechanisms for the realization of the nephrotoxicity of anticancer drugs, as well as various forms of its clinical and laboratory manifestations. Summing up, it should be emphasized that risk factors for the development of kidney damage in cases of MNs and during their management are the cumulative dose of the chemotherapy agent, the total dose of the agent accumulated over all received courses of chemotherapy, drug administration regimens, the combination of several nephrotoxic medications, hypovolemia, anemia, presence of comorbid pathologies, as well as concomitant diseases of the urinary tract and tumor infiltration.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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