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Cancer screening and treatment in patients with end-stage renal disease: remaining issues in the field of onco-nephrology

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Abstract

Onco-nephrology is a rapidly growing field that has recently garnered significant attention. Although the risk of developing cancer is reported to be higher in patients with end-stage renal disease (ESRD) than in the general population, the screening protocol and the treatment of cancer in ESRD patients have not yet been established. Recent studies have suggested that cancer screening in dialysis patients would be ineffective from a cost and survival benefit perspective. Nevertheless, the ESRD population is heterogeneous, including patients of varying age and comorbidity, and it is essential to identify those who would benefit from cancer screening. Once patients with ESRD are diagnosed with cancer, anti-cancer treatment should be initiated. However, a treatment strategy has not yet been established. Although many drugs require dose adjustments in hemodialysis patients, data on the pharmacokinetics of anti-cancer agents in these patients remain scarce. This review addresses the recent evidence of cancer risk and screening in the ESRD population and the pharmacokinetics of anti-cancer agents in hemodialysis patients.

Keywords: Onco-nephrology, Cancer risk, Cancer screening, Pharmacokinetics, Dialysis, End-stage renal disease

Background

Onco-nephrology is a new and evolving subspecialty that connects two different areas, oncology and nephrology. Improvement in cancer therapies has led to an increase in the number of cancer survivors, some of whom develop acute and chronic kidney complications. A better understanding of cancer-associated kidney complications, such as paraneoplastic glomerulopathies and chemotherapy-associated kidney diseases, is thus required to enable oncologists and nephrologists to treat patients suffering from cancer and kidney disease [1–3]. The term “onco-nephrology” usually relates to acute and chronic kidney complications that arise due to cancer or cancer treatment. In order to provide evidence-based care for patients with cancer and kidney disease, however, the issues on how to manage cancer in patients with end-stage renal disease (ESRD) should be incorporated into the field of onco-nephrology. As discussed below, two important issues remain unsolved in this field (Table 1).

The first issue relates to cancer screening in patients with ESRD. Since patients with ESRD are at a higher risk of cancer than the general population [4, 5], there is an urgent need to establish cancer-screening protocols for patients with ESRD. Previous studies have failed to demonstrate a substantial increase in life expectancy from cancer screening in patients with ESRD [6, 7]. These studies reported that this conclusion should be tempered when cancer screening is applied to individual patients, however, since the ESRD population is heterogeneous, and includes patients who are expected to have a long life expectancy as well as patients with a limited life expectancy as a result of advanced age or severe comorbidities. In order to establish ways to identify individuals who should receive cancer screening in this population, the frequency of cancer, the cost and effectiveness of screening tests, and patient life expectancy all need to be taken into consideration.

The second issue is that it is essential to establish treatment recommendations for ESRD patients diagnosed with

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Table 1 Areas of special importance in the field of onco-nephrology

Areas	Comments
	The representative areas in (A)~(C) can be described as follows (the details were reviewed previously [1]).
(A) Acute kidney injury in cancer patients	The causes of AKI in cancer patients can be categorized as prerenal, intrinsic, and postrenal.
	• Prerenal (extracellular fluid depletion, hypercalcemia, hepatic sinusoidal occlusive syndrome, drugs)
	• Intrinsic (acute tubular necrosis, lymphomatous infiltration of the kidney, cast nephropathy, tumor lysis syndrome, thrombotic microangiopathy, secondary glomerulopathies)
	• Postrenal (extrarenal obstruction due to primary disease, retroperitoneal lymphadenopathy, retroperitoneal fibrosis)
(B) Paraneoplastic glomerulopathies	• Solid malignancy-associated membranous nephropathy
	• Hematologic malignancy-associated minimal change disease
(C) Chemotherapy-associated kidney manifestations	• Minimal change disease and focal segmental glomerulosclerosis (interferon, pamidronate)
	• Acute tubular necrosis and electrolyte wasting (cisplatin)
	• Magnesium wasting (cetuximab)
	• Thrombotic microangiopathy (bevacizumab, tyrosine kinase inhibitors, and gemcitabine)
	• Cast nephropathy (methotrexate)
(D) Cancer risk and screening in patients with ESRD	Although the etiologies of cancer-associated renal diseases in (A)~(C) are relatively well understood, the protocols of the cancer screening and effective anti-cancer treatment for ESRD patients are not established yet.
(E) Anti-cancer chemotherapy in patients with ESRD	

cancer. The coexistence of ESRD with cancer reduces the likelihood that cancer patients will receive optimal anti-cancer therapy and supportive care. Chemotherapy might be withheld because they are undergoing hemodialysis (HD). A lack of information concerning chemotherapy in patients with ESRD also leads to the improper use of anti-cancer agents and severe adverse effects in these patients [8]. Data on renal or dialysis clearance for these agents remain scarce, although the number of case studies that include pharmacokinetic data and information related to the safety and efficacy of these agents has gradually increased in recent years. It is essential to find dose adjustment models and to modify existing chemotherapy protocols adequately for HD patients.

This review updates the information on cancer screening and the pharmacokinetics of anti-cancer agents in patients with ESRD.

Cancer risk in patients with ESRD

Observational studies have suggested an increased cancer risk in patients with ESRD [9, 10]. Patients on chronic dialysis have an increased risk of cancer for several reasons, including the presence of chronic infection, a compromised immune system, nutritional deficiencies, and altered DNA repair [5]. There are also predisposing factors that contribute to the higher incidence of certain cancers in dialysis patients. Acquired renal cystic kidney disease increases the risk of renal cell carcinoma [11]. Long-term use of analgesics is a risk factor for transitional cell carcinoma of the bladder, ureter, and renal pelvis and for renal cell carcinoma [11–13]. In addition, the use of prolonged oral cyclophosphamide is a risk factor for bladder cancer [14]. Notably, there is an increased risk of several infection-associated cancers, such as the liver, cervix uteri, and tongue [5, 15–17]. The higher prevalence of infection with hepatitis B and C and human papillomavirus in HD patients probably accounts for the increased risks of these cancers [18–20]. In contrast, it remains controversial whether the risk of cancer of the lung, stomach, colon, breast, and corpus uteri is increased in patients with ESRD [5, 15–17]. In Japan, the most common cancer in ESRD patients is renal cell carcinoma, and the second is multiple myeloma, followed by liver and colon cancer in males and uterine cancer in females [21]. In contrast, while the most common cancer in ESRD patients in the USA is renal cell carcinoma as is in Japan, the second is prostate cancer in males and breast cancer in females [22]. In addition, whether cancer risk differs between transplant periods (under immunosuppression) and periods of dialysis after transplant failure (when immunosuppression is ceased or reduced) was investigated in a retrospective cohort of 8173 kidney transplant recipients [23]. In the multivariate analysis, incidences of non-Hodgkin lymphoma, lip cancer, and melanoma, which were included in infection- or immune-related cancers, were lower during dialysis after transplant failure whereas the incidence of thyroid cancer, which was shown to be included in ESRD-related cancer, was lower during periods of transplant function. More recently, a larger retrospective study including 202,195 kidney transplant candidates and recipients also examined whether cancer risk changes between

transplant periods and periods of dialysis [22]. Due to the large sample size, this study provided more precise estimates of many individual cancers. In this study, individuals with transplants had higher adjusted risks of Kaposi sarcoma; non-Hodgkin lymphoma; Hodgkin lymphoma; melanoma; and cervical, anal, vaginal/vulvar, penile, otopharyngeal, liver, stomach, lung, lip, and non-epithelial skin cancers (which were included in infection- or immune-related cancers) than those with nonfunctioning kidneys on waiting lists and those with graft failure. In contrast, individuals with nonfunctioning kidneys had higher adjusted risks of kidney and thyroid cancers, which were considered to be related to ESRD. These studies indicated that the risk of infection- or immune-related cancers was higher in transplant recipients with functioning kidneys whereas the risk of ESRD-related cancers was higher in those under dialysis following kidney failure.

Cancer screening in the ESRD population

Standard malignancy-screening recommendations are based on the assumption that those screened would have a normal life span. It must be taken into consideration that benefit may be reduced or absent in individuals with low life expectancy. There is a general agreement that routine cancer screening is unlikely to result in a net benefit for individuals with limited life expectancy [24, 25]. This is reflected in the existing guidelines for various kinds of cancer, although different guidelines recommend different life expectancies or age cutoffs for cessation of cancer screening [26]. In the ESRD population, the expected remaining lifetime of most dialysis patients is shorter than the time lived after a cancer diagnosis, making cancer screening ineffective in terms of cost and survival benefit [27, 28]. In a cost-effectiveness analysis that compared cancer screening in patients on HD with screening in the general population, the screening benefits of mammography, Papanicolaou tests, flexible sigmoidoscopy, and serum prostate-specific antigen (PSA) levels were denied for the following reasons [6]: First, the costs per unit of survival benefit conferred by cancer screening were 1.6 to 19.3 times higher in patients with ESRD compared with those in the general population. Second, the net gain of life expectancy in patients with ESRD via these screening programs was calculated to be 5 days or less. Based on these results, it was concluded that routine cancer screening in the ESRD population was a relatively ineffective allocation of financial resources. Similar findings were also shown in a study evaluating the efficacy of breast and cervical cancer screening of Canadian women on HD [7].

It is important to recognize that the results obtained in these studies are average results for the ESRD population. It must not be concluded that no HD patients need cancer screening. Life expectancy for patients on dialysis would be better in the absence of coexisting complications, for example. In addition, malignancy is a common cause of death in patients receiving dialysis. In Japan, the percentage of HD patients who died of malignancies was 9.1 % in total causes of death, ranking third after cardiac failure (27.2 %) and infectious diseases (20.3 %) [29]. It should also be noted that patient survival in Japan has been better than that in the Western countries [30]. In addition, the magnitude of the association between mortality and cancer was greater in Japan than in Europe or the USA [30]. One cannot ignore the significant benefit to a patient who is diagnosed with a malignancy at an early stage by cancer screening and who could potentially receive curative therapy. These screening tests seem to be better limited to individualized patients with risk factors for malignancy and long life expectancy. The difference in cancer incidence between kidney transplant recipients and dialysis patients with nonfunctioning kidneys also suggests a need to individualize cancer screening [22, 23]. In the CANcer and DialYsis (CANDY) study including 178 patients on chronic HD who subsequently had cancer, the mean and median times for cancer development after dialysis initiation were 30.8 and 13 months, respectively [8]. These results may indicate that cancer screening should be performed not long after the beginning of dialysis sessions, especially within the first few years. Further studies would help to establish cancer-screening protocols.

Although cancer-screening protocols in patients with ESRD have not been established, the efficacy of tumor markers has been relatively well examined in the ESRD population. Tumor markers have been used to follow the clinical course of certain cancers and also used as cancer-screening tools (Table 2). Since many tumor markers are not removed effectively by HD due to the relatively high molecular weight, serum levels are elevated after HD as a result of hemoconcentration, limiting their clinical effectiveness [31–33]. Total PSA, the sum of free and complex PSA, is used as a screening test for prostate cancer, usually in combination with digital rectal and ultrasound-guided examination. The percent of free PSA (fPSA) in total PSA (tPSA) is also used to enhance the discrimination of prostate cancer because the percent of fPSA is lower in men with prostate cancer than that in men with benign disorders [34]. tPSA is valid in dialysis patients, although fPSA is elevated and should not be used as a screening test for prostate cancer in dialysis patients [35]. Cancer antigen 125 (CA-125) is a tumor marker for ovarian cancer but is also produced by mesothelial cells [36]. Serum CA-125 levels are elevated in HD patients with serosal fluid, pleural effusion, ascites, etc., and the results should be interpreted with caution [37]. In particular, this marker is a less

Table 2 Summary of tumor markers in dialysis patients (modified from [31])

Tumor marker	Comments
(A) Reliable in dialysis patients	
Total prostate-specific antigen (tPSA)	Free PSA (fPSA) could be filtered through glomeruli, consistent with its low molecular weight (28 kDa). Decreased GFR leads to an increased serum level of fPSA and higher percent fPSA to tPSA (%fPSA), since the level of tPSA does not differ compared with that of the controls [35]. Although not eliminated by low-flux membranes, fPSA is cleared by high-flux membranes [76], since molecules smaller than 5 and 50 kDa are filtered by low-flux and high-flux dialysis membranes, respectively [39].
β-human chorionic gonadotropin (β-hCG), α-fetoprotein	
(B) Falsely elevated in dialysis patients	
Cancer antigen 125 (CA-125)	CA-125 is elevated in patients with peritoneal, pleural, or pericardial effusion [37]. In particular, CA-125 is falsely elevated as a result of nonspecific peritoneal irritation or peritonitis in patients undergoing peritoneal dialysis [38]. The serum concentration of CA-125 is increased during hemodialysis, probably due to hemoconcentration [32].
Carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), squamous cell carcinoma (SCC) antigen, and neuron-specific enolase (NSE)	Although the metabolism and clearance are not fully understood, previous studies revealed that the serum levels of CA19-9, CEA, SCC, and NSE are elevated in dialysis patients compared with patients with normal renal function [39–42]. An increase in the serum levels of these tumor markers is also found during hemodialysis, probably as a result of hemoconcentration [32]. It should be noted that SCC is cleared by high-flux membranes due to its molecular weight of 42 to 48 kDa, although it is not eliminated by low-flux membranes [33].

GFR glomerular filtration rate

accurate indicator of disease burden in patients undergoing peritoneal dialysis, since serum levels may be falsely elevated as a result of nonspecific peritoneal irritation or peritonitis [38]. Carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), squamous cell carcinoma (SCC) antigen, and neuron-specific enolase (NSE) have also been reported to be falsely elevated in dialysis patients compared with patients with normal renal function [39–42]. In contrast, α-fetoprotein and β-human chorionic gonadotropin are reliable tumor markers in dialysis patients [43].

Although increased risks of colorectal and breast cancer have not been established in the ESRD population, as stated above, it has been emphasized that the results of fecal occult blood tests and mammography in patients with ESRD should be interpreted with caution. A positive stool guaiac test occurs at a higher frequency in dialysis patients due to an increased incidence of nonmalignant gastrointestinal abnormalities. In one series, the incidence of guaiac positive stools was three times higher in asymptomatic dialysis patients compared with non-ESRD controls [44]. However, the presence of a positive stool test in asymptomatic patients may enable the early detection of colorectal cancer. Mammography, a low-dose x-ray system for examination of the breasts, aids in the earlier detection of breast cancer. The presence of benign vascular calcification in women with ESRD complicates mammography and leads to higher rates of false-positive results [45]. Since these cancers do not appear to be more common in patients with ESRD, patients on transplant waiting lists and patients with predisposing risk factors and long expected survival would be appropriate candidates for these screenings.

Pharmacokinetics of anti-cancer agents in patients on hemodialysis

Chemotherapy can be challenging when the patient's renal function is compromised. Although most anticancer agents are eliminated through the kidney, data on renal or dialysis clearance of these agents are scarce and often incomplete. The available recommendations for the appropriate dose adjustment of these agents for the ESRD population are based on data from a small series of case reports and expert opinions [46]. Many cytotoxic agents are excreted predominantly in the urine unchanged or as active/toxic metabolites. Thus, any reduction in renal clearance may result in the accumulation of potentially toxic components and overdose. For anuric HD patients, although the renal toxicity of chemotherapeutic agents is not a problem, the patients are exposed to all other potential dose-related systemic adverse effects. In addition, previous pharmacokinetic studies indicated that changes in the non-renal drug clearance occur in patients with ESRD [47]. Drug-metabolizing enzymes and transporters in other organs are considered to be affected by kidney diseases [47]. The influence of renal insufficiency on the renal and non-renal drug clearance of anti-cancer agents remains incompletely understood. The CANDY study included 178 patients on chronic HD who subsequently had cancer and 50

patients (28 %) who had received anti-cancer drug treatment. Most of the patients received at least one anti-cancer agent for which specific attention was required in terms of drug dosage adjustments (72 %) and adequate timing of administration (82 %) [8]. A total of 44 % of the treated patients developed iatrogenic toxicity: 34 % related to drugs requiring dosage adjustment and 17 % related to additional drugs with no existing management recommendations in dialysis patients. These results indicated that the lack of evidence concerning the use of systemic anti-cancer agents in renal insufficiency could lead to the inappropriate use of chemotherapy and fatal toxic effects in these patients. Although the pharmacokinetics of several chemotherapeutic agents in HD patients has been relatively well examined in case studies, the dose and timing of administration remain under debate. Previous case studies have examined different doses and intervals between HD and drug administration. HD immediately after dialyzable drug administration may improve tolerance although such protocols may lead to the reduction of anti-neoplastic efficacy and impose excess burden on the patient and treatment teams. In addition, a limited number of facilities can offer both HD and anti-cancer treatment on the same day. These limitations might deprive the patient of opportunities to receive optimal anti-cancer treatment. These social factors must also be taken into consideration in the establishment of anti-cancer therapeutic protocols.

This section focuses on the relatively well-described anti-cancer agents used in HD patients that have different main elimination organs, carboplatin (mainly eliminated by the kidney) and 5-fluorouracil (5-FU) (mainly eliminated by the liver), as well as tyrosine kinase inhibitors, that are frequently used in this new era of targeted anti-cancer therapy.

Carboplatin

One of the most widely used anti-cancer agents in HD patients is a platinum derivative, carboplatin [48, 49]. In patients with normal renal function, approximately 70 % of the administered dose is excreted in the urine [50]. It has been shown that the target area under the curve (AUC) of carboplatin is associated with myelosuppressive and cytotoxic effects. Therefore, in clinical practice, the Calvert formula is well accepted for calculating the dose of carboplatin: dose (mg) = AUC (mg/ml × min) × (glomerular filtration rate [GFR] (ml/min) + 25) [50]. For patients with ESRD, many clinicians still use this formula with the assumption that the GFR can be almost equal to zero [51–53]. This AUC-targeted dose adjustment has permitted the individualization of the carboplatin dose for maximum effect with tolerable adverse effects. The HD setting after the administration of carboplatin influences the concentration of carboplatin in the plasma, since carboplatin can be removed from the plasma by HD [48]. The interval between the administration of carboplatin and HD varied between 1 and 24 h in previous studies (Table 3). In these studies, the AUCs varied depending on the doses and intervals between drug infusion and HD. Although there were variations between studies, the AUCs seemed to be higher when HD was started long after carboplatin infusion. A certain amount of carboplatin can be eliminated by performing HD in an early phase when the protein binding ratio is low [54]. This dialyzability may help to improve tolerance, although actual AUC values may be less reliable and more unstable when HD is performed immediately after the administration [51]. The protein binding of carboplatin, which hinders its elimination in HD, has been observed to increase by 50 % after 24 h of administration [54]. Oguri et al. reported that the actual AUC values were approximately 20 % higher than the target AUC when HD was performed 24 h after the administration of carboplatin [51]. Particular attention should be paid to the development of adverse events such as hematological toxicities when there is a long interval between carboplatin administration and HD.

5-FU

5-FU is mainly metabolized via redihydropyrimidine dehydrogenase in the liver and other tissues, and only a small amount of 5-FU (approximately 10 % of the administered dose) is eliminated unchanged by the kidney [55]. In line with its short elimination half-life (20 min), 5-FU is given by intravenous continuous infusion over several days as well as by intravenous bolus infusion, allowing the easy determination of systemic clearance based on steady-state plasma concentrations [56]. In a previous case report, a weekly regimen composed of CPT-11 (50 mg/m^2) followed by leucovorin (10 mg/m^2) and 5-FU (400 mg/m^2) was administered immediately after HD. Although the dose of 400 mg/m^2 5-FU was reduced compared with that of patients with normal renal function, the bolus intravenous injection of 5-FU to HD patients after HD sessions provided a blood concentration profile similar to that in normal subjects [57]. The patient presented with grade 3 hematological toxicity that was recovered by granulocyte colony-stimulating factor. In another study, the intravenous bolus and continuous infusion of 5-FU was included in the FOLFOX 4 regimen; the doses of oxaliplatin and 5-FU were both reduced from those in the original FOLFOX 4 regimen. The dose of oxaliplatin was 40 mg/m^2, and 5-FU was given as a bolus of 300 mg/m^2 followed by a continuous intravenous infusion of 500 mg/m^2 [58]. HD was performed 1 h after the administration of oxaliplatin on day 1 and was repeated 2 days later after the completion of

Table 3 Intervals between carboplatin infusion and HD and AUCs of free carboplatin in previous studies of carboplatin-based chemotherapy in HD patients

	Number of patients	Disease	Carboplatin dose	Interval between carboplatin infusion and hemodialysis (h)	AUC (mg × min/ml) of free carboplatin
(A) Hemodialysis was initiated soon after carboplatin infusion (1~2 h after infusion).					
Kurata et al. (1994) [77]	1	Ovarian carcinoma	240 mg/m^2 (cycle 1)	1	3.14
			240 mg/m^2 (cycle 2)	2	5.09
Suzuki et al. (1997) [78]	1	Merkel cell carcinoma	150 mg (cycle 1)	1	4.6
			150 mg (cycle 2)	2	4.8
Watanabe et al. (2002) [52]	1	Ovarian carcinoma	125 mg (cycle 1)	1.5	2.21
Furuya et al. (2003) [79]	1	Urothelial carcinoma	125 mg	1	2.44
Takezawa et al. (2008) [80]	1	SCLC	250 mg/m^2 (cycle 1)	1	4.10
			275 mg/m^2 (cycle 2)	1	4.16
Kamata et al. (2009) [81]	1	NSCLC	150 mg/m^2	1	4.9
Yoshida et al. (2009) [82]	1	Ovarian carcinoma	125 mg	1	0.98
Kondo et al. (2012) [83]	1	Cancer of unknown primary	125 mg (cycle 1)	1	3.03
			125 mg (cycle 2)	1	3.44
			125 mg (cycle 3)	1	3.5
Hiraike et al. (2012) [54]	1	SCLC	480 mg (cycle 1)	1	13.45
			170 mg (cycle 2)	1	5.74
(B) Hemodialysis was initiated long after carboplatin infusion (16~24 h after infusion).					
Motzer et al. (1990) [84]	2	Germ cell tumor	100 mg/m^2	24	6.7
		Germ cell tumor	100 mg/m^2	24	6.9
Chatelut et al. (1994) [48]	1	Ovarian carcinoma	100 mg (cycle 1)	24	3.5
			150 mg (cycle 2)	24	6.7
			150 mg (cycle 3)	24	6.06
Watanabe et al. (2002) [52]	1	Ovarian carcinoma	125 mg (cycle 2)	16	4.43
			125 mg (cycle 3)	16	4.75
			125 mg (cycle 4)	16	4.13
Yokoyama et al. (2006) [85]	1	Ovarian carcinoma	200 mg (cycle 1)	24	8.03
			200 mg (cycle 2)	16	5.69
Oguri et al. (2010) [51]	2	NSCLC	100 mg	24	4.7
		Ovarian cancer	125 mg	24	6.1
Kodama et al. (2010) [86]	1	Ovarian carcinoma	100 mg (cycle 1)	24	3.48
			150 mg (cycle 2)	24	4.23
			175 mg (cycle 3)	24	5.55
			150 mg (cycle 4)	24	4.59

SCLC small cell lung cancer, *NSCLC* non-small cell lung cancer

drug administration. Vomiting (grade 2), anorexia, and leukopenia (both grade 3) were observed after the first treatment. A total of four courses were administered thereafter by reducing the dose of oxaliplatin to 32 mg/m^2, the intravenous bolus of 5-FU to 240 mg/m^2, and the continuous infusion of 5-FU to 400 mg/m^2. After the dose reduction, no adverse events were observed other than anorexia (grade 1). Although the dose reduction of 5-FU was not recommended in previous studies [46, 59, 60], these studies indicated that a further accumulation of cases is needed to establish the optimal dose in HD patients. Particular attention should also be paid to the development of 5-FU-induced encephalopathy, especially when a higher dose of 5-FU is administered. Ammonia, a metabolite of 5-FU, accumulates in large amounts after the administration of high-dose 5-

FU [61, 62]. Renal dysfunction may be an aggravating factor of hyperammonemia related to 5-FU infusion [63, 64]. It has been suggested that a large amount of fluoroacetate, a final metabolite of 5-FU, could be accumulated in patients with renal dysfunction and inhibit the Krebs cycle. This could cause impairment in the ATP-dependent urea cycle, resulting in lactic acidosis and further exacerbation of a hyperammonemic state [62, 64]. The direct toxicity of alpha-fluoro-beta-alanine (FBAL), an intermediate metabolite of 5-FU, on myelin was also proposed as the cause of 5-FU-induced encephalopathy [65]. In HD patients, FBAL, which is mainly excreted by the kidney with minor elimination via bile and the bowel, was reported to accumulate approximately twofold higher than expected in patients with normal renal function [66]. The authors also reported that FBAL could be eliminated by HD, suggesting that more intensive dialysis treatment may be useful for improving the elimination of FBAL to minimize the possible risks of FBAL-mediated toxicity.

Tyrosine kinase inhibitors

Several studies have recently examined the pharmacokinetics of tyrosine kinase inhibitors such as sunitinib, imatinib, sorafenib, and erlotinib in HD patients [67–71]. After oral administration, these agents are primarily metabolized in the liver by cytochrome CYP3A4, with only a small proportion excreted in the urine [72, 73]. These agents were reported to be minimally affected by HD [67, 69–71]. Therefore, administration can take place anytime, independent of the HD sessions. Previous studies have shown that treatment with these agents is well tolerated and has good efficacy in patients with ESRD [71, 72, 74, 75]. However, one study showed that dose reduction or discontinuation of sorafenib was frequently needed (even with lower concentrations of sorafenib) in patients with metastatic renal cell carcinoma undergoing HD [70]. Serious adverse events were found in 9 of 10 patients, including a grade 5 subarachnoid hemorrhage and a grade 4 cerebellar hemorrhage. The authors suggested that the patients on chronic HD might be susceptible to the unfavorable effects of anti-angiogenic agents like sorafenib due to their vulnerable vascular tissues. Treatment of HD patients with tyrosine kinase inhibitors appears to be feasible, but special attention should be paid to the occurrence of serious adverse events, considering the underlying risk factors of HD patients.

Conclusions

Since a growing number of patients with ESRD are developing cancer, it is essential to establish evidence-based recommendations for cancer screening and anti-cancer treatment in the ESRD population. This review provided recent evidence for cancer risk and screening in the ESRD population. There is a pressing need for clinical trials that are designed to identify those who would benefit from cancer screening in this population. This review article also addressed the pharmacokinetics of representative anti-cancer agents, carboplatin, 5-FU, and tyrosine kinase inhibitors. Although the optimal interval between dialysis sessions and carboplatin infusion has not been fully investigated, the usefulness of the administration of carboplatin to HD patients has been documented in previous reports, in which the dose was calculated by the Calvert formula, assuming the GFR to be zero. While the dose reduction of 5-FU may not be recommended in previous studies, the metabolites of 5-FU such as ammonia, fluoroacetate, and FBAL can be accumulated in HD patients, indicating the need for the reassessment of the optimal dose of 5-FU in HD patients. Although treatment with tyrosine kinase inhibitors at the same dose as in normal subjects is often feasible in HD patients, it should be kept in mind that HD patients might be more susceptible to adverse effects due to underlying risk factors. The data are limited, mostly consisting of single case studies that have examined different chemotherapy protocols. Future studies employing the same regimen for larger patient populations are warranted. The accumulation of studies will lead to the establishment of optimal therapeutic strategies for patients suffering from cancer and kidney disease.

Competing interests

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Authors' contributions

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