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Management of patients with end-stage renal disease undergoing chemotherapy: recommendations of the Associazione Italiana di Oncologia Medica (AIOM) and the Società Italiana di Nefrologia (SIN)

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ABSTRACT

Background The overall risk of some cancers is increased in patients receiving regular dialysis treatment due to chronic oxidative stress, a weakened immune system and enhanced genomic damage. These patients could benefit from the same antineoplastic treatment delivered to patients with normal renal function, but a better risk/benefit ratio could be achieved by establishing specific guidelines. Key considerations are which chemotherapeutic agent to use, adjustment of dosages and timing of dialysis in relation to the administration of chemotherapy.

Methods We have reviewed available data present in the literature, including recommendations and expert opinions on cancer risk and use of chemotherapeutic agents in patients with end-stage renal disease. Experts selected by the boards of the societies provided additional information which helped greatly in clarifying some issues on which clear-cut information was missing or available data were conflicting.

Results Data on the optimal use of chemotherapeutic agents or on credible schemes of polychemotherapy in haemodialysed patients are sparse and mainly derive from case reports or small case series. However, recommendations on dosing and timing of dialysis can be proposed for the most prescribed chemotherapeutic agents.

Discussion The use of chemotherapeutic agents as single agents, or in combination, can be safely given in patients with end-stage renal disease. Appropriate dosage adjustments should be considered based on drug dialysability and pharmacokinetics. Coordinated care between oncologists, nephrologists and pharmacists is of pivotal importance to optimise drug delivery and timing of dialysis.

INTRODUCTION

Worldwide, the number of patients receiving long-term haemodialysis (HD) is estimated at more than 1 million, with the incidence

Key questions

What is already known about this subject?

► In the literature, information regarding this issue is sparse and mainly derives from case reports or small case series.

What does this study add?

► Our study, reviewing published papers with the help of experts selected by the boards of the Italian Society of Medical Oncology and the Italian Society of Nephrology (which helped greatly in clarifying some issues) provides practical recommendations for the management of patients with cancer with end-stage renal disease undergoing chemotherapy.

How might this impact on clinical practice?

► The paper may impact on the everyday clinical practice by supporting clinical decisions in a setting where no recommendations are available from Medical Oncology societies.

growing annually.¹ Significant improvements in chronic renal replacement therapy have led to prolonged survival, which has resulted in an increased risk of malignancy. Other than their extended lifespan, patients with end-stage renal disease (ESRD) are at increased risk of cancer for several reasons, including the presence of chronic infection, weakened immune system, nutritional deficiencies and altered DNA repair.²

There are no established guidelines on how to administer most of the cytotoxic substances employed in the treatment of cancer to dialysed patients. Because of the impaired renal function, dosage reduction of anticancer drugs is often recommended to avoid adverse drug reactions. On the other hand, if an anticancer drug is removed significantly by

HD or is not eliminated through the kidney, dose reductions may reduce the therapeutic efficacy. In some cases, dialysis must be precisely timed in conjunction with chemotherapy (CT) administration, to avoid toxicity.³ Pharmacokinetic data concerning the relationship between dialysis and chemotherapeutic drugs are lacking of well-designed studies, most of the data are limited to case reports and small case series.^{4,5}

MATERIALS AND METHODS

We reviewed available data present in the literature, including recommendations and expert opinions on cancer risk and use of chemotherapeutic agents in patients with ESRD. In addition, experts selected by the boards of the Societies, who are listed among the authors, provided additional biological and clinical information which helped greatly in clarifying some issues in the absence of clear-cut information from the literature.

RESULTS

Chronic dialysis and cancer risk

Increased cancer risk in patients with ESRD occurs after kidney transplantation and during dialysis.^{6–8} However, the standardised mortality ratio is similar to general population, except for kidney cancer, which have a higher cancer mortality risk in dialysis patients.⁹

A significant trend emerges, demonstrating an increased risk of occurrence of at least some types of cancer. Renal cancer shows the highest incidence rates (in most of available studies >3.0). Bladder, liver, thyroid, oral cavity and cervical cancer incidence also increase, although to a lesser extent. Some high-incidence forms of cancer, such as breast, lung, prostate and colon cancer do not seem to have an increased risk of occurrence in patients undergoing HD.³

During prolonged dialysis treatment, carcinogenesis may be triggered by different biological conditions, including both cell-mediated and humoral impairment of immunity, resulting in a greater susceptibility to oncogenic viral infections as demonstrated by an increased incidence of Human Papillomavirus (HPV), Human Herpesvirus 8 (HHV-8) and Epstein-Barr Virus (EBV)-related malignancies.⁸ Some studies have also shown an increase in genomic damage in dialysis patients resulting from a dysfunction in the DNA repair mechanisms, reduced antioxidant activity characteristic of chronic renal failure,⁹ accumulation and release of uremic toxins during dialysis procedures, increased production of inflammatory cytokines with genotoxic properties (eg, tumour necrosis factor). Carcinogenesis may also be related to the underlying renal disease: acquired renal cystic disease is a risk factor for renal cell carcinoma, and renal disease secondary to analgesic abuse is a risk factor for transitional cell cancer of the urinary tract.^{10–13}

Chemotherapy in ESRD

There are three main aspects that must be taken into consideration when proposing CT to a patient undergoing HD: (i) selection of the agent(s); (ii) dosage adjustment; (iii) timing of dialysis in relation to the administration of CT. The loss of renal function in HD patients leads to increased exposure to the risk of overdosing of some CT drugs. On the other hand, the dialysis procedure can remove an excessive amount of drug, exposing the patient to ineffective doses.³ This latter consideration applies to the dialysable drugs whose administration time must be scheduled immediately after the dialysis session. On the other hand, infusion of CT should precede the dialysis when it is necessary to remove the amount of drug that is not distributed in target tissues and which may cause side effects.

In 1990, Sauer *et al.*¹⁴ published the results of an in vitro pharmacokinetics study of 20 chemotherapeutic agents. They classified them into 'good, intermediate and ineffective' according to their dialysability. Although this represents valuable information (update of the dialysability of chemotherapeutic agents can be found at <http://www.drugbank.ca/>), the pharmacodynamics of drugs, in vivo, can be influenced by many variables that are not reproducible in vitro. Drugs with a molecular weight <1000 Da can diffuse through membranes and their removal is markedly affected by their binding to plasma proteins and their volume of distribution. Those agents that mainly bind to plasma proteins are poorly dialysable due to the high molecular weight and structure assumed by the complex drug-protein. In patients with severe renal impairment, the reduction of plasma proteins may therefore increase the concentration of free drug, increasing its elimination.¹⁵ Chemotherapeutic agents with a large volume of distribution are less dialysable than those with low volume of distribution, which tend to remain confined to the intravascular compartment. Elimination through dialysis is also influenced by the transfer rate of the drug from tissues to plasma. An estimate of this parameter can be obtained by the plasma half-life: the shorter the half-life, the higher the rate of transfer and consequently the dialysability of the drug. Another factor that must be taken into account concerns the transformation of drugs into active or inactive metabolites that may have different pharmacokinetic characteristics compared with the parent drug.¹⁶

Considering the number and complexity of the factors that play a role in the dialysis of drugs, the application of parameters that can estimate the real in vivo elimination would be extremely useful.

The HD clearance of a substance cannot be simply deduced from that observed in patients with preserved renal function. According to Janus *et al.*,³ there are three useful indices to evaluate the influence of HD on the pharmacokinetics of chemotherapy agents. The first two are represented by the HD clearance, understood as the removal rate related to blood concentration when entering the dialyser and the coefficient of extraction

Table 1 Recommendations on the management of the clinical frequently used chemotherapeutic agents in patients undergoing dialysis according to Janus *et al*³ and Tomita *et al*¹⁶

Drug	Dose adjustment	Timing of administration
5-Fluorouracil	Standard dose	After HD
Capecitabine	Limited data to recommend its use*	No data
Carboplatin	AUCx25	Non-dialysis day
Cisplatin	Reduction of 50%–75%	After HD
Cyclophosphamide	Reduction of 25%	After HD
Docetaxel	65 mg/m ²	Before or after HD
Doxorubicin	Standard dose	After HD
Epirubicin	Standard dose	After HD
Etoposide	Reduction of 40%–50%	Before or after HD
Gemcitabine	Standard dose	6–12 hours before HD
Ifosfamide	Not recommended	
Irinotecan	Reduced dose: 50 mg/m ² /week	After HD
Methotrexate	Reduction of 75%†	After HD
Oxaliplatin	Reduction of 30%	After HD
Paclitaxel	Standard dose	Before or after HD
Vinorelbine	Reduction of 25%–33%	After HD

*Reduction by 50% proved safe in two patients.

†Limited data, not recommended.

AUC, area under the curve; HD, haemodialysis.

indicated by the percentage of drug removed from the blood by the dialyser. These two parameters, together, measure the ability of the dialysis system to remove the drug from the blood, but cannot be extrapolated from the clinical setting. The third parameter, named F_{HD} , was proposed by Launey-Vacher *et al* in 2005.¹⁷ It was derived from a formula that took into account the amount of drug effectively removed by dialysis, but its relationship to the amount eliminated through the process of extrarenal removal, still active in dialysis patients. F_{HD} represents the contribution of dialysis to the overall elimination of a substance. Launey-Vacher believes that if F_{HD} of a drug is <25%, the HD clearance is insignificant compared with the total body clearance and the administration of the drug can be programmed independently of the dialysis session schedule. On the other hand, when F_{HD} exceed 25% the drug should be administered after the dialysis.

Management of single chemotherapeutic agents

The literature on the use of many antineoplastic agents in HD is limited to a few case reports or small case series, or is

entirely absent. There is stronger evidence supporting the correct mode of administration, for those drugs that are more widely used in clinical practice. Table 1 compares the recommendations provided in two of the most authoritative reviews on the management of the most frequently used drugs in patients undergoing HD.^{3–17}

PLATINUM SALTS

Cisplatin is predominantly eliminated through the kidney (about 90%). Its plasma concentration decays with a typical biphasic pattern characterised by a rapid initial clearance (half-life <1 hour) followed by a much slower drop (half-life between 58 and 73 hours).¹⁸ In addition, cisplatin rapidly forms a strong and irreversible bond with plasma proteins.⁴ Consequently, patients with ESRD are exposed to potential dose-dependent side effects, so dose adjustments are required. Since the pharmacological effects of cisplatin depend on the amount of time it stays in the intravascular compartment, Tomita *et al*¹⁶ recommend a dose adjustment and administration immediately preceding the HD session. In contrast, since the rapid elimination of free cisplatin during dialysis is not compensated by the portion of the drug complexed with protein, Janus *et al* recommend the administration of a reduced dose of 25%–50%, after dialysis.³ Several studies have demonstrated the efficacy of, and tolerance to, cisplatin administered in doses between 25 and 80 mg/m² every 2, 3 or 6 weeks.^{19–20}

Renal elimination of *carboplatin* contributes 95% to its complete removal. Pharmacokinetic studies in patients with normal renal function have shown that 65% of the drug is excreted in the urine within 12 hours. Binding with plasma proteins occurs in the first 24 hours, but the complexed portion is not metabolically active, so only the free portion influences the effectiveness and toxicity of the treatment.²¹ Carboplatin is the only drug whose dosage should not be calculated in relation to body surface but should be based only on pharmacokinetics. For patients with renal impairment, the dose administered in order to reach the area under the curve (AUC) is lower and the reduction is related to the rate of creatinine clearance, calculated according to the Calvert formula. In patients undergoing HD, the glomerular filtration rate (GFR) is close or equal to 0 and the dose that can be safely administered is AUCx25 mg.²¹ It has been demonstrated that the removal of carboplatin by HD was well tolerated; therefore, several authors have recommended to plan the administration of carboplatin on a non-dialysis day.²²

Elimination of *oxaliplatin* is mostly via the kidney and the rate of removal by dialysis is estimated to exceed 80%.²³ In patients with renal impairment, the pharmacokinetics are altered. The clearance of the drug, as well as the AUC, appear to be related to GFR. However, some studies seem to indicate that pharmacokinetic alterations are not accompanied by equally significant pharmacodynamic changes in patients with CrCl >20 mL/min, dose adjustments are not deemed necessary.²⁴ The recommended

dose of oxaliplatin for patients on dialysis has not yet been established. Some authors have evaluated its use in polychemotherapy with doses between 40 and 85 mg/m², but the results, in terms of both effectiveness and safety, are not unequivocal.²⁵ Given its high dialysability, oxaliplatin should be administered after dialysis or in a day without dialysis. In most case reports analysed, HD was performed soon after the administration of oxaliplatin and the dosing interval was extended to 3 weeks. Janus *et al*, while not recommending its use in ESRD, unless essential, suggest a dose reduction of 30%.³

NUCLEOSIDE ANALOGUES

The elimination of 5-fluorouracil (5-FU) takes place through catabolism in the liver and other tissues and, to a lesser extent, by urinary excretion. The pharmacokinetics of 5-FU and its metabolites have been investigated in several studies which showed no significant differences from patients with preserved renal function.^{26–27} The results in terms of effectiveness and safety appeared satisfactory. Therefore, 5-FU can be administered in the usual doses, preferably after the dialysis session.

Capecitabine is a prodrug converted in the liver first into 5-deoxy-5-fluorocytidine, and subsequently into 5-deoxy-5-fluoridina (5-DFUR). The 5-DFUR is activated to 5-FU, in tumour tissues.

The use of capecitabine in patients with GFR <30 mL/min is contraindicated based on a phase II study that showed an increased incidence of adverse events of grade 3 and 4 in this subgroup of patients.²⁸ The only data on the use of capecitabine in patients on HD derive exclusively from a retrospective study on 12 patients with renal failure, including two patients who progressed to ESRD and were started on HD while on therapy with capecitabine. In these two patients, capecitabine at a reduced dose of about 50%, was well tolerated and effective.²⁹ The paucity of evidence does not allow any kind of recommendation.

Gemcitabine (2',2'-difluorodeoxycytidine), is a prodrug metabolised to its cytotoxic metabolites by intracellular phosphorylation. Intravenously administered gemcitabine is rapidly metabolised to a non-cytotoxic metabolite, dFdU.³⁰ The renal elimination of gemcitabine and its metabolites contributes <10% and 90%, respectively, to their complete removal. In the few case reports published on the use of gemcitabine in patients on HD, the toxicity observed was generally comparable to that seen in patients with normal renal function. Pharmacokinetic parameters of gemcitabine were not altered, but a higher AUC of dFdU and its metabolites were found in a patient on HD, suggesting a correlation between higher risk of toxicity, reduced dFdU elimination and high intracellular concentrations of the phosphorylated metabolites.³¹ However, the same study confirmed the efficacy of HD in reducing plasma concentrations of dFdU. Some case series concerning gemcitabine as a single agent or in combination with cisplatin suggest that to reduce the risk of gemcitabine-related side effects, HD should be initiated within 6–12 hours after gemcitabine infusion.^{32–33}

ANTHRACYCLINES

Most of the available studies regarding the use of *doxorubicin* in patients on HD have been conducted in haematological disorders.³⁴ In this setting, the drug is administered at standard doses without toxicity. Doxorubicin and its major metabolite, doxorubicinol, are poorly metabolised by the kidney, although it has been shown that the two compounds exhibit an increased AUC in patients with renal insufficiency.³⁵ Doxorubicin may not need dose adjustment and the administration should be done after, or on a day without, HD.

The liver is the main route of elimination of *epirubicin*, a second-generation anthracycline. Renal excretion is <9%. To the best of our knowledge, only one case report of weekly epirubicin in a patient with breast cancer on HD has been published. The treatment was safe and effective.³⁶

ALKYLATING AGENTS

Cyclophosphamide is inactive until processed by the liver into a number of active metabolites (at least 6). Both the metabolites and the remaining fraction of unaltered drug are eliminated through the kidneys. Its use in patients on HD has been the object of several studies with conflicting results. Haubitz *et al*³⁷ evaluated the administration of cyclophosphamide with a dose of 0.5–1 g/m² in haemodialysed patients. Twenty-two per cent of the drug was eliminated within 3 hours after the start of the dialysis with an average total clearance lower than that observed in subjects with normal renal function. For this reason, a dose reduction of 30% is recommended. Because of its dialysability, cyclophosphamide may be infused after HD.

Approximately 40% of an *etoposide* dose is excreted by the kidneys. Most studies investigating the pharmacokinetics of etoposide in patients on HD have shown parameters comparable to those of patients with normal renal function. Watanabe *et al*³⁸ reported on a dose-escalation study of etoposide at a starting dose of 50 mg/m² in association with cisplatin, and before HD, in five patients. Toxicity was manageable and the standard dose was considered feasible in patients on HD. However, other studies have observed a rise of the AUC and a prolonged half-life of etoposide, suggesting that a dose reduction of etoposide is necessary in order to avoid haematological toxicity.³⁹ On the basis of these data, a dose reduction of 50%–60% should be recommended in patients on HD. Etoposide is not removed by HD and it can be used before or after HD sessions.

Ifosfamide is primarily metabolised by the liver. The prodrug is transformed to an active phosphoramidate mustard, but also generates the urotoxin acrolein, and the neurotoxin and nephrotoxin, chloroacetaldehyde. In vitro studies suggest that HD can decrease ifosfamide concentrations by 87% and chloroacetaldehyde by 77%. Pharmacokinetic data on clearance of ifosfamide in patients on HD are limited and controversial. Carlson *et al*⁴⁰ evaluated ifosfamide in an anephric patient, and observed that chloroacetaldehyde-associated neurotoxicity

Table 2 Multiagent chemotherapy regimens feasible in patients undergoing dialysis (modified from ref. 3)

Cancer type	Chemotherapy regimen	Dosage proposed	Timing of dialysis
Lung			
	CDDP+VNR	CDDP (25–50 mg/m ²) day 1 + VNR (20 mg/m ² /week) days 1, 8	1 hour after CT, daily
	CBDCA+VNR	CBDCA (AUC x 25) day 1 + VNR (20 mg/m ² /week) days 1, 8	12–24 hours after CT
	CBDCA+DXL	CBDCA (AUC x 25), DXL (65 mg/m ²) day 1	12–24 hours after CT
	CDDP+GEM	CDDP (25–50 mg/m ²) day 1 + GEM (800 mg/m ²) days 1, 8	1 hour after CDDP
	CDDP+TXL	CDDP (25–50 mg/m ²) day 1 + TXL (175 mg/m ²) day 1	1 hour after CDDP
	CBDCA+ETP	CBDCA (AUC 5x25) day 1 + ETP (50–100 mg/m ²) days 1, 3	12–24 hours after HD
	CDDP+ETP	CDDP (25–50 mg/m ²) day 1 + ETP (50–100 mg/m ²) days 1, 3	1 hour after CDDP
	No available data supporting the use of pemetrexed		
GI cancer			
	FOLFOX6	OX (40–50 mg/m ²), 5-FU and LV reduced by 70%–80%	1 hour after OXA infusion, 2 days later
	5-FU+LV	Standard dose	after CT
	CDDP+5-FU	CDDP (25–50 mg/m ²) day 1, 5-FU (500 mg/m ² i.c.) day 1–5	1 hour after CDDP, every 2 days
	FOLFOXIRI bevacizumab	Standard dose reduced by 30%	1 hour after CPT-11 infusion, 2 days later
	FOLFIRI	CPT-11 (180 mg/m ² and 125 mg/m ²), 5-FU standard dose	1 hour after CPT-11
Breast cancer			
	Epirubicin+CTX	Epirubicin standard dose+CTX reduced of 25%	24 hours after CT
	Epirubicin+TXL	Standard dose	24 hours after CT
	FEC75	Epirubicin and 5-FU standard dose+CTX reduced of 25%	24 hours after CT
Germ cell tumours			
	CDDP+ETP	CDDP (14–20 mg/m ²), ETP (50–100 mg/m ²) days 1–4	Daily or on days 2 and 4
	CBDCA+ETP	CBDCA (100 mg/m ²) day 1, ETP (50–100 mg/m ²) days 1–4	On days 2 and 4
	On the basis of available data, the use of ifosfamide and bleomycin is not recommended		
Urothelial cancer			
	TXL+GEM	TXL (175 mg/m ²) day 1+GEM (800 mg/m ²) days 1, 8	24 hours after CT
	CBDCA+TXL	CBDCA (AUC 5x25) day 1 + TXL (175 mg/m ²) days 1, 8	24 hours after CBDCA
	CBDCA+GEM	CBDCA (AUC 5x25) day 1 + GEM (800 mg/m ²) days 1, 8	24 hours after CBDCA
	M-VAC	MTX (15 mg/m ²), CDDP (40 mg/m ²), VLB (1.8 mg/m ²), DX (18 mg/m ²) day 1	1 hour after CDDP
	VAC	CBDCA (100 mg/m ²), VLB (3 mg/m ²), DX (22.5 mg/m ²) day 1	24 hours after CBDCA

CDDP, cisplatin; VNR, vinorelbine; DXL, docetaxel; TXL, taxol; ETP, etoposide; FOLFOX6, fluorouracil (FU), oxaliplatin (OXA), leucovorin (LV); FOLFOXIRI: FU, OXA, irinotecan, LV; FEC, FU, epirubicin, cyclophosphamide; GEM, gemcitabine; CT, chemotherapy; i.c., continuous infusion; M-VAC, methotrexate, vinblastine, doxorubicin, CDDP.

improved rapidly after chemotherapy infusion. In keeping with these data, Tomita *et al*¹⁶ recommended that ifosfamide should not be used in patients with severe renal impairment, whether or not it is intended to use dialysis. Recently, Latcha *et al*⁴¹ reported the outcomes for three patients on HD who received titrated doses of ifosfamide (starting dose of 1.5 mg/m²). Myelosuppression was the most common side effect, but no patient

developed life-threatening toxicity and the authors concluded that ifosfamide can be used safely. Data on the use of ifosfamide in patients on dialysis are too limited and controversial to support clear-cut recommendation.

ALKALOID ANALOGUES

Paclitaxel is metabolised by cytochrome P450 in the liver. The renal contribution to the removal of paclitaxel is insignificant. Several small studies confirm its pharmacokinetics do not differ significantly in patients with ESRD compared with those with preserved renal function.^{42 43} The tested dosages of paclitaxel vary between 150 and 300 mg/m². The results are satisfactory both in terms of efficacy and tolerance. Therefore, no dosage adjustments are needed and the timing of dialysis is unimportant.

Also for *docetaxel*, the main metabolic pathway is hepatic and only a small part of administered drug is recovered unchanged in the urine. Several case reports have been published on the use of the drug as a single agent, or in combination regimens, for the treatment of patients on HD.^{44 45} For use in combinations, Janus *et al* recommend the use of a reduced dose of 65 mg/m². Since the drug is non-dialysable, the administration may take place either before or after the dialysis procedure.³

Irinotecan is converted to an active metabolite, SN-38. Urinary excretion accounts for <20% of the elimination of the administered dose. Many authors have emphasised the necessity for reduced dosage in patients with ESRD based on case reports showing grade 4 toxicities or deaths after receiving irinotecan in combination with 5-FU.⁴⁶ In another case report, the authors reported an effective dose-reduced protocol with irinotecan (50 mg/m², 80 mg total, weekly) with no grade 3/4 toxicities. Since it appeared to be well tolerated, the dose was increased up to 100 mg/m², but at this dosage severe diarrhoea (grade 4) appeared.⁴⁷ A reduced weekly dosage of 50 mg/m² of irinotecan might therefore be more appropriate, preferably after HD sessions or on non-dialysis days.⁴⁸

Multiagent chemotherapy patients with specific cancer diseases

A variety of combination chemotherapy regimens and dialysis schedules are described in literature and newer chemotherapeutic agents are usually excluded. Despite the limitations associated with these publications, and the possible bias in favour of cases with positive outcome, the case reports represent a starting point to define possible multiagent chemotherapy regimens to offer dialysis patients. Table 2 reports combination regimens that can be reasonably proposed for patients with ESRD.

DISCUSSION

The overall risk of cancer is increased in patients with ESRD. A considerable number of these patients could benefit from antineoplastic treatment, but the management of CT in such population is a particularly challenging issue.

In patients with cancer and undergoing dialysis, the decision to initiate an anticancer treatment should be based on a discussion of prognosis and therapy options for both conditions. Haemodialysed patients have an overall life expectancy shorter than the normal population and

Box 1 Recommendations on the use of chemotherapeutic agents in cancer patients with end-stage renal disease (ESRD) undergoing dialysis

- ▶ Patients with ESRD undergoing chemotherapy need coordinated care between oncologists, nephrologists and pharmacists to optimise drug delivery and timing of dialysis.
- ▶ The decision to initiate an anticancer treatment should be based on a discussion of prognosis and therapy options for both conditions. Frailty scores, like in oncogeriatrics, should be built to optimally adapt cancer treatments in these dialysis patients.
- ▶ Drug clearance by dialysis must be taken into account for appropriate chemotherapy timing in order to avoid drug removal, which may result in a loss of efficacy.
- ▶ Chemotherapeutic agents without or with limited renal excretion (ie, taxanes and anthracycline) can be given at full doses in patients with ESRD.
- ▶ Drugs predominantly eliminated through the kidney, such as cisplatin, should be substituted when equally effective and more manageable agents are available (ie, carboplatin).
- ▶ Multiagent chemotherapy is feasible in ESRD; it must be cautiously checked before administration with appropriate dosage adjustment whenever necessary also based on the limited literature in this setting.

the quality of life is already heavily affected by renal replacement therapy. Consequently, it is important when selecting patients, to consider the realistic goal of treatment ('adjuvant', 'curative' or 'palliative'), the tumour-related and the renal disease-related life expectancy, the impact of CT on the quality of life and patient characteristics such as age, performance status, frailty and comorbidities.

Data regarding the optimal use of chemotherapeutic agents in this patient population are sparse and mainly derive from case reports or small case series. For some newer drugs, with an already extensive clinical use, such as pemetrexed, there are no data. The lack of knowledge about cytotoxic drug management may lead to an improper use of CT and may expose patients to the risk of suboptimal treatment or to aggravation of chemotherapy toxicity. However, for some clinical settings the use of chemotherapeutic agents as single agents, or in combination, can be safely proposed in patients with ESRD. A summary of the Associazione Italiana di Oncologia Medica and the Società Italiana di Nefrologia recommendations, including suggestions for patient selection is reported in Box 1.

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