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Management of targeted therapies in cancer patients with chronic kidney disease, or on haemodialysis: An Associazione Italiana di Oncologia Medica (AIOM)/Societa' Italiana di Nefrologia (SIN) multidisciplinary consensus position paper

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ABSTRACT

The increasing availability of novel biological anticancer agents has greatly improved the outcome of several cancer patients; unfortunately, data regarding efficacy, safety and pharmacokinetics of many of these agents in patients with chronic renal disease or on hemodialysis are scanty. Furthermore these results are controversial and a treatment strategy has not yet been established. Therefore, the Associazione Italiana di Oncologia Medica and the Società italiana di Nefrologia undertook the present work aiming at providing health professionals with a tool for easier clinical management of target therapies in this setting of patients. A web-based search of MEDLINE/PubMed library data published from 2000 to June 2018 has been performed. More than one hundred papers, including recommendations and expert opinions, were selected and discussed by the authors. A panel of experts provided additional biological and clinical information, helping in clarifying some issues in the absence of clear-cut information from the literature.

1. Introduction

Chronic kidney disease (CKD) is a clinical condition defined as the presence of abnormalities of kidney structure or function, that has existed for at least 3 months, with implications for patient's health. According to the most recent classification of Kidney Diseases Improving Global Outcomes (KDIGO) classification (Table 1), CKD is classified according to cause, glomerular filtration rate (GFR), and albuminuria, in 5 stages (from very mild damage in stage 1 to kidney failure or end-stage renal disease [ESRD]) (Levey et al., 2011).

CKD and cancer are illnesses that coexist in an increasing number of patients potentially affecting both cancer treatment, as well as overall prognosis (Launay-Vacher V et al., 2007). The Renal Insufficiency and Anticancer Medications (RIAM) Study Group showed that more than half of the patients with an active malignancy concomitantly have an estimated GFR lower than 90 ml/min/1.73m^2. Furthermore, the prevalence of stage 3–5 CKD not requiring hemodialysis (HD) was 11.8–12.0% (Launay-Vacher et al., 2007; Launay-Vacher, 2010) while about 5% of HD patients had a concomitant diagnosis of cancer (Chien et al., 2017). Despite these figures, the approach to cancer patients with

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Table 1
Classification of CKD according to KDIGO.

Stage of CKD	Qualitative Description	eGFR (mL/min/1.73 m^2)
1	Kidney damage-normal GFR	≥90
2	Kidney damage-mild reduction GFR	60-89
3	Moderate reduction GFR	30-59
4	Severe reduction GFR	15-29
5	Kidney Failure – ESRD	< 15 or hemodialysis

CKD, Chronic kidney disease; ESRD, end-stage renal disease; KDIGO, Kidney Diseases Improving Global Outcomes; GFR, glomerular filtration rate.

ESRD to HD is highly subjective, greatly varying among physicians and countries.

The likelihood that CKD or HD patients could receive an optimal anti-cancer treatment remains an unsolved clinical issue. Similarly unsolved are issues relative to dosage adjustment according to pharmacokinetic (PK) and pharmacodynamic (PD) parameters, as well as the timing of drug administration with respect of HD session.

For this reason, in 2015 the European Medicines Agency (EMA) issued an updated version of its guidelines on the evaluation of PK of drugs in patients with decreased renal function, encouraging clinical investigation in this population (EMA Guideline, 2015).

There is existing evidence supporting the optimal management of chemotherapeutic agents in this subset of patients (Pedrazzoli et al., 2017). However, although the PK of new several targeted therapy agents is often well known, data on HD clearance, and consequently recommendation on dose and timing of administration, are mostly limited to single case reports and small case series.

ESRD may alter the PK of drugs during the processes of absorption, distribution, metabolism, elimination or excretion, due to biochemical alterations (i.e., hypoalbuminemia, presence of edema, metabolic acidosis, abnormal enteric drug metabolism, or reabsorption) (Czarnecka et al., 2015; Janus and Launay-Vacher, 2017; Arantes et al., 2018).

On the other hand, HD could result in an early elimination of the drug, with potential under-dosage and consequently loss of efficacy. This clinical issue appears to be even more complex in HD patients treated with oral therapies twice or three times a day.

Overall, it would be the crucial element in defining both the dose adjustment and the optimal time of administration of each given drug, with regards to the HD session. Dose adjustments can be made by reducing the unit dose (dose method), increasing the interval between administrations (interval method), or the association of both of them (mixed method) (Janus et al., 2013).

For these reasons, the Associazione Italiana di Oncologia Medica (AIOM) and the Società italiana di Nefrologia (SIN) undertook the present work with the aim to provide practical tools for the management of targeted therapies in CKD or HD cancer patients.

2. Materials and methods

A web-based search of MEDLINE/PubMed library data published from 2000 to June 2018 was performed by associating each molecule listed below with “renal insufficiency” OR “renal imparment” OR “chronic kidney disease” OR “end stage renal disease” OR “hemodialysis OR “dialysis” and “cancer”. More than one hundred papers, including recommendations and expert opinions, were selected by the authors. Each paper was retrieved and its references were reviewed to identify additional studies.

A panel of experts provided additional biological and clinical information, which helped greatly in clarifying some issues in the absence of clear-cut information from the literature.

The final draft was then submitted to the evaluation of experts and

Table 2
General indications (according to EMA and including orphan drug designations) for antiangiogenic agents and dose adjustment recommendations for patients with CKD and on HD.

Monoclonal antibodies		Indication (as monotherapy or in combination)	Dose reduction required?		
			Patients with mild to moderate CKD	Patients with severe CKD	Patients on dialysis
	Bevacizumab	• Colorectal cancer • NSCLC • Breast cancer • Kidney cancer • Ovarian cancer	No	No data	No
	Ziv-Aflibercept	• Colorectal cancer	No	Limited data	No data
	Ramucirumab	• Gastric cancer • Colorectal cancer • NSCLC	No	Limited data	No data
MATKIs					
	Sorafenib	• Kidney cancer • HCC • Differentiated thyroid cancer	No	No	Limited data
	Axitinib	• Kidney cancer	No	No data	Limited data
	Sunitinib	• GIST • Kidney cancer • pNET	No	No	No
	Pazopanib	• Kidney cancer • soft-tissue sarcomas	No	Limited data	Limited data
	Cabozantinib	• Kidney cancer	Suggested	No data	No data
	Regorafenib	• Colorectal cancer • GIST • HCC	Mild CKD: no. Moderate CKD: no data	No data	Limited data
	Nintedanib	• NSCLC	No	No data	No data
	Lenvatinib	• Differentiated thyroid cancer • HCC	No	Suggested	No data
	Vandetanib	• Medullary thyroid cancer	Mild CKD: no. Moderate CKD: suggested	No data	No data
	Apatinib	• Gastric cancer	No	No data	No data

CKD, Chronic kidney disease; MATKIs, multi-targeted antiangiogenic tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; GIST, gastrointestinal stromal tumors; pNET, pancreatic neuroendocrine tumors.

modified according to their suggestions and comments.

3. Anti-angiogenics

Antiangiogenic agents are either monoclonal antibodies targeting circulating vascular endothelial growth factor (VEGF) or VEGF receptors (VEGFRs), or small molecules tyrosine kinase inhibitors targeting mainly VEGFRs and therefore called multi-targeted anti-angiogenic tyrosine kinase inhibitors (MATKIs). General EMA indications for the use of these agents are reported in Table 2, together with the recommendation for dose reduction depending on the severity of kidney impairment.

Monoclonal antibodies are eliminated via catabolism by lysosomal degradation to peptides and amino acids. The high molecular weight of monoclonal antibodies makes it impossible for the kidneys to eliminate them, unless there is a presence of pathologic conditions. Indeed, fragments which could be filtered are re-absorbed and metabolized in the proximal tubule of the nephron (Ryman and Meibohm, 2017). Thus, renal toxicity is mainly related to the intrinsic mechanism of the action of the drug on the VEGF/VEGFRs pathway (Cosmai et al., 2017). Despite all of what has been stated above, the safety and efficacy of ***bevacizumab*** (Avastin®) in clinical trials have not been investigated in patients with renal impairment (RI). Clearance of bevacizumab was seen rather to be influenced by low levels of serum albumin (≤ 29 g/dL), with a 20% faster elimination than in patients with normal values (Avastin, 2019). Gupta et al reported the safety and efficacy of bevacizumab at 10 mg/kg every 2 weeks in 5 mRCC patients with RI (i.e. CrCl < 60 ml/min). Only 1 patient required a dose reduction, and the incidence of toxicities was not different in RI, compared to normal renal function patients, unless for larger median increases in blood pressure (Gupta et al., 2011).

Bevacizumab has been also used at a dose of 5 mg/kg every 14 days in HD patients (Garnier-Viougeat et al., 2007; Inauen et al., 2007). The PK parameters obtained from one patient treated with this dosage were equivalent to those of subjects with normal renal function receiving 10 mg/kg every 14 days (Garnier-Viougeat et al., 2007). Since this drug has a molecular weight of 149 kDa, it is not dialyzable and it may be administered anytime before or after HD session (Avastin, INN-bevacizumab - Europa EU).

Similarly, the renal elimination of ***ziv-aflibercept*** (Zaltrap®), another high molecular weight protein, is expected to be minimal. A PK analysis was conducted on 549 patients with a ClCr between 50 and 80 ml/min, 96 patients with a ClCr between 30 and 50 ml/min and 5 patients with a ClCr < 30 ml/min). This analysis suggests that no dose adjustment is required for ziv-aflibercept in the first two groups of patients, whilst no conclusions can be drawn for patients with ClCr < 30 ml/min, due to the very limited sample size, although the exposure to the drug was similar to that seen in patients with normal renal function. No clinical data are available regarding the management of ziv-aflibercept in HD patients (Zaltrap, 2019).

The metabolism of ***ramucirumab*** (Cyramza®) has not been studied, although a mechanism similar to the one described for the other two monoclonal antibodies here reported is likely to be seen. Furthermore, there have been no formal studies to evaluate the effect of RI on its PK. Based on the population-PK analysis, the manufacturer reported that drug exposure was similar in patients with mild, moderate and severe RI, as compared to patients with normal renal function (CYRAMZA, 2019). Therefore, dose adjustments are not required in these populations, although once again no solid data are available to extend these findings to severe dysfunction (O'Brien et al., 2017). Unfortunately, no data are avaible for HD patients.

As far as MATKIs are concerned, they show mainly hepatic metabolism. However, although insignificant, the amount of the drug excreted by the kidneys may greatly vary between different agents of the same family. Generally speaking, data present in literature suggest a good tolerability and efficacy of these agents in ESRD patients. Furthermore, they can be administered without considering the timing of the HD sessions (Kennoki et al., 2011).

Following oral administration, ***sorafenib*** (Nexavar®) is metabolised mainly in the liver by both CYP3A4 and glucuronidation, while urinary excretion represents a minor share (19%) of the elimination (Lathia et al., 2006). There are conflicting literature data about PK and optimal dosage of sorafenib in patients with kidney disease. Miller et al. characterized PK and a tolerable dose of sorafenib in patients with renal dysfunction (n = 52), including one HD cohort (n = 17). The authors observed no significant changes in PK after administration of a single dose of 400 mg in patients with different degrees of RI. A second phase of the study was aimed at determining its maximum tolerated dose. Results in terms of tolerance suggested an empiric sorafenib starting dose of 400 mg twice a day in patients with CrCl between 40 and 59 mL/min, 200 mg twice a day in CrCl between 20 and 39 mL/min, and 200 mg each day in HD population. Dose escalation was suggested only if the drug was well tolerated (Miller et al., 2009). There are other PK studies that point out an increase in sorafenib plasma concentration during HD session (Hilger et al., 2009; Kennoki et al., 2011; Shinsako et al., 2010). On the other hand, sorafenib administered at a standard dose of 400 mg twice daily was well tolerated for a patient undergoing HD, with drug plasma concentration similar to that reported in patients with normal renal function. These data suggest that the same dosage of sorafenib might be safely administered to patients undergoing HD as well as patients with normal renal function (Ferraris et al., 2009; Maroto Rey and Villavicencio, 2008; Ruppin et al., 2009; Shinsako et al., 2010). On the contrary, Leonetti et al. performed a systematic review regarding PK and clinical outcomes of sorafenib in 36 HD renal cell carcinoma patients. Authors concluded that it is not possible to exclude a major exposure to sorafenib in HD, due to both efficacy and toxicity profiles which were more relevant than expected. Therefore, they suggested that therapy start with reduced doses (i.e. 400 mg/die) (Leonetti et al., 2016). Although the manufacturer does not recommend any dose adjustment for patients with any level of renal insufficiency (Nexavar, 2019), assessment of which is based on available dose-limiting toxicity data, a reduced starting dose seems reasonable with the possibility of a dose escalation in relation to tolerance and clinical effectiveness. Furthermore, the drug should be administered, as a precaution, after the HD.

Axitinib (Inlyta®) is metabolised mainly by CYP3A4/5 and, secondly, by CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT)1A1. Following hepatic metabolization, its elimination occurs by feces, whereas renal excretion accounts for < 20% (Bellesoeur et al., 2017). There are few clinical data on axitinib treatment in RI patients. PK and safety appeared to be not affected by renal dysfunction in a pharmacokinetic population study (Thiery-Vuillemin et al., 2017; Chen et al., 2016). The summary of product characteristic does not recommend dose adjustment in subjects with RI but no data are available for patients with a CrCl of < 15 mL/min (Inlyta, 2019). The high level of protein binding (> 99%) impacts on drug filtration during HD sessions, making it difficult to determine its optimal dose, athough the rate of drug removed by HD is meaningless (< 0.62%) (Nishida et al., 2016). Axitinib has been administered at the dose of 6 mg/day, with a subsequent increase to 10 mg/day, in one HD patient, and at a starting dose of 5 mg twice a day in another HD subject (Nishida et al., 2016). No difference in terms of PK, safety, and clinical outcomes were observed (Thiery-Vuillemin et al., 2017). These data would suggest to start with the standard 5 mg twice a day dose also in ESRD or HD, a dose which could be increased in case of good toxicity profile. However, it should be considered that a dose titration study clearly demonstrated that increased axitinib doses increased overall response rates in the absence of an impact on PFS (Rini et al., 2013).

Sunitinib (Sutent®) is primarily metabolized in the liver by CYP3A4, with only up to 16% of the drug excreted in urine (Houk et al., 2009; Speed et al., 2012). Several studies suggested that PK of sunitinib in subjects with CrCl < 30 ml/min is similar to those with normal renal

function (Thiery-Vuillemin et al., 2011). The standard starting dose of sunitinib (50 mg o.d. for 4 weeks followed by a 2-week break) appears to be tolerated by patients with RI (Khosravan et al., 2010). HD was reported not to affect plasma concentration, as the compound is non-dialyzable. Thus, it may be administered any time before or after HD. PK studies analyzing sunitinib in HD patients reported mean concentrations within its therapeutic range (50–100 ng/ml), as well as in an area below the plasma concentration-time curve (AUC) similar to patients without renal insufficiency (Izzedine et al., 2009). Several case reports and retrospective studies demonstrate the efficacy and tolerability of sunitinib, given at different doses within the classical 4:2 schedule, in HD patients (Josephs et al., 2011; Masini et al., 2012). Because a clear correlation between drug exposure and treatment efficacy has been demonstrated (Houk et al., 2010), dose reductions should be avoided as much as possible, in order to maximize both activity and efficacy (Porta et al., 2014).

Pazopanib (Votrient®) is mainly metabolized in the liver by CYP3A4 and excreted in feces with a renal elimination of < 4%. Therefore, no dose adjustment is required in patients with CrCl > 30 ml/min. The shorter half-life (31 h) compared to sunitinib (80–110 hours) gives this drug a greater manageability due to the low probability of accumulation in patients with kidney impairment. PK and clinical data for patients with CrCl < 30 ml/min are still an unmet focus. The limited PK data available for 1 HD patient suggest that no dose adjustment is necessary in this setting (Noda et al., 2016). Nevertheless, Bersanelli et al. (2016) reported a small series of HD patients treated with pazopanib who required significant reductions in dose as a consequence of toxicity. Considering all the 11 patients assessed, only 6 started at the full dose of 800 mg o.d., and 3 of them needed a dose reduction (two to 600 mg, and one to 400 mg); 4 other patients started at the dose of 600 mg per day, and required a dose reduction to 400 mg; the remaining case, after starting treatment at the dose of 400 mg, was able to escalate to 800 mg.

Cabozantinib (Cabometyx® or Cometriq®) displays a long term plasma half-life (˜120 h) and accumulates ˜five fold by day 15 following daily dosing based on AUC. Its AUC was increased by 7–30% in subjects with mild/moderate RI. The plasma half-life of cabozantinib is 99 h. The drug and its metabolites are excreted in the faeces (54%), as well as in the urine (27%). Results from a study in patients with RI indicate that the C_{max} and $AUC_{0\text{-}inf}$ were 19% and 30% higher for subjects with mild RI, and 2% and 6–7% higher, for subjects with moderate RI, respectively, compared to subjects with normal renal function (Lacy et al., 2017). Cabozantinib should thus be used with caution in subjects with mild or moderate RI, while it is not recommended for patients with severe RI. No data are avaible in HD patients (Cabometyx, 2019).

Regorafenib (Stivarga®) is metabolized primarily in the liver by oxidative metabolism mediated by CYP3A4, as well as by glucuronidation mediated by UGT1A9 (Rey et al., 2015). Urinary excretion of glucuronides decreases from 19% to less than 10% under steady-state conditions. When regorafenib was administered to patients with mild RI, no clinically significant differences in the mean exposure of regorafenib or its metabolites were noted. There are limited data on patients with moderate RI and no data on those with severe RI or ESRD (Regorafenib (Stivarga), 2019). A pharmacokinetics and safety study of regorafenib in cancer subjects with severe RI is currently ongoing (NCT, 01853046).

Bolonesi et al. described a metastatic colorectal cancer patient treated with regorafenib while on HD. Although the patient tolerated a regorafenib dose of 40 mg daily for 21 days, the treatment was interrupted after one cycle of treatment because of a septic shock and the worsening of cardiomyopathy (Bolonesi et al., 2014). This case clearly suggests that great caution is needed when using this agent in the HD setting.

As far as ***nintedanib*** (Vargatef®), less than 1% is excreted via the kidney (Vargatef, 2019). Adjustment dose in patients with mild to moderate RI is not required. The safety and pharmacokinetics of nintedanib have not been studied in patients with severe RI or on HD (Vargatef, 2019). Although it proved able to revert established renal fibrosis through the inhibition of renal pro-inflammatory cytokines expression and macrophage infiltration (Liu et al., 2017), another report suggested the possibility that it could induce acute anti-glomerular basement membrane glomerulonephritis (Ismail et al., 2017).

No adjustment of starting dose is required for ***lenvatinib*** (Lenvima®) in patients with mild or moderate RI. In patients with severe RI, the recommended starting dose is 14 mg taken once daily considering further dose adjustments based on individual tolerability. In fact, subjects with baseline renal injury had higher grade 3 and 4 toxicities incidences (eg hypertension, proteinuria, fatigue, stomatitis, thrombocytopenia, prolonged QT, etc.) compared to normal renal function patients. No data are available for ESRD or on HD. (Lenvima, 2019). Notably, this MATKI proved able to induce different renal adverse events, either focal segmental glomerulosclerosis (Furuto et al., 2018), thrombotic microangiopathy (Hyogo et al., 2018), or renal failure as a whole (Cavalleri et al., 2018).

As far as ***vandetanib*** is concerned (Caprelsa®), a PK analysis in subjects with kidney failure showed that exposure is increased by about 46%, 62% and 79% in subjects with mild, moderate and severe RI, respectively (Weil et al., 2010). However, clinical data do not suggest any change in the starting dose in patients with mild RI, whereas a reduction of starting dose to 200 mg is suggested in patients with moderate RI. Vandetanib is not recommended for use in patients with severe RI since there are limited data on the safety and efficacy in this category of patients (Caprelsa, 2019). No clinical data are available concerning its use in patients on HD. Interestingly, vandetanib inhibition of some human renal transporters (MATE1 and MATE2K) explains some reports of decreased CrCl, and increased cisplatin nephrotoxicity in subjects treated with this MATKI (Shen et al., 2013).

Finally, no data are available regarding the use ***apatinib*** in the case of severe kidney impairment, although its metabolites are minimaly excreted (7%), and there is evidence of negligible quantities of unchanged apatinib in urine (Ding et al., 2013).

4. EGFR-pathway inhibitors

Available EGFR inhibitors presently include three monoclonal antibodies (cetuximab, panitumumab and necitumumab) and five small-molecule tyrosine kinase inhibitors (TKIs – gefitinib, erlotinib, afatinib, dacomitinib and osimertinib) (Saxena et al., 2011; Holleman et al., 2019; Quatrale et al., 2011). General EMA indications for the use of these agents, together with recommendation for their dose reduction depending on the severity of kidney impairment, are reported in Table 3.

As usual, clinical trials testing activity and safety of these compounds have generally excluded patients with ESRD. A few case reports of patients treated with anti-EGFR therapies while receiving HD have been published (Aldoss et al., 2009; Fontana et al., 2014). These data suggest that ***cetuximab*** (Erbitux®) is safe and effective in this setting and that dose reductions are not needed in HD patients. Another report analyzing the PK of cetuximab showed that it could be safely used in patients with renal injury without dose adjustment (Krens et al., 2014).

Panitumumab (Vectibix®) clearance in HD has not yet been analyzed. Due to the molecular size, panitumumab, as cetuximab, is not excreted in the urine, in that it is cleared by the reticuloendothelial system. In a population PK analysis (Ma et al., 2009) concomitant CKD did not show an impact on its PK. Panitumumab was safely administered in a small number of patients with ESRD or on HD without the need for dose reductions (Kobayashi et al., 2016; Krens et al., 2018).

No data are available relative to the use of ***necitumumab*** (Portrazza®) in patients with kidney impairment or on HD.

In population PK studies, no significant correlations have been shown between CrCl and clearance of EGFR TKIs, suggesting that dose modifications are not necessary in patients with mild to moderate CKD.

Table 3
General indications (according to EMA and including orphan drug designations) for EGFR inhibitors and dose adjustment recommendations for patients with CKD and on HD.

Monoclonal antibodies		Indication (as monotherapy or in combination)	Dose reduction required?		
			Patients with mild to moderate CKD	Patients with severe CKD	Patients on dialysis
TKIs	Cetuximab	• Colorectal cancer • Head and neck cancers	No	No	No
	Panitumumab	• Colorectal cancer	No	No	No
	Necitumumab	• NSCLC	No	No data	No data
	Gefitinib	• NSCLC	No	No data	Limited data
	Erlotinib	• NSCLC • Pancreatic cancer	No	No data	Limited data
	Afatinib	• NSCLC	No	No	Limited data
	Dacomitinib	• NSCLC	No	No data	No data
	Osimertinib	• NSCLC	No	No data	No data

CKD, Chronic kidney disease; TKIs, tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer.

The use of these drugs, however, is not recommended in patients with severe CKD for whom data are (as usual) unavailable (Porta et al., 2015). From those few case reports on the use of ***gefitinib*** (Iressa®) during HD, it seems that the drug is not dialysed, with almost 90% of it remaining in the plasma after HD (Del Conte et al., 2014).

A small study compared PK of ***erlotinib*** (Tarceva®) and its active metabolite desmethyl erlotinib in 3 HD patients and 5 patients with normal renal function. Renal function and HD had only slight effects on the PK, and the safety and efficacy of erlotinib were maintained (Togashi et al., 2010).

Four cases of HD lung cancer patient treated with ***afatinib*** (Giotrif®) have been reported so far; in the first patient reported, a 25% dose reduction was required from the start of treatment, with good safety and efficacy profiles (Bersanelli et al., 2014). In the other 3 patients, PK data were available. All of them were administered 30 mg afatinib daily with dialysis three times a week. All 3 patients exhibited a partial response without any serious adverse events during the administration of afatinib, while PK data proved to be similar to those of patients with normal organ function (Imai et al., 2017). Based on population pharmacokinetic analysis of data derived that adjustments to the starting dose in patients with mild, moderate or severe renal failure are not necessary, but patients with severe impairment should be monitored (Giotrif, 2019).

Even though there are some reports available regarding the use of ***osimertinib*** (Tagrisso®) in patients with chronic kidney disease or on dialysis (Tamura et al., 2017; Iwafuchi et al., 2017; Yamada et al., 2018), no data can be found in the literature regarding ***dacomitinib*** (Vizimpro®).

5. Anti-HER2 agents

These agents are represented either by monoclonal antibodies (trastuzumab, pertuzumab or Trastuzumab Emtansine – T-DM1) or by TKIs (lapatinib and neratinib). General EMA indications for the use of these agents, together with recommendation for their dose reduction depending on the severity of kidney impairment, are reported in Table 4.

According to the results of population PK analyses, no dosage adjustments for these agents are recommended in patients with mild to moderate CKD. Unfortuntaly, the need for dose adjustment in patients with severe renal injury cannot be determined, owing to a lack of data. However, as a whole, kidney impairment or HD shouldn't support the interruption or the lack of indication of an active anti-HER anticancer treatment (Cosmai et al., 2015).

Trastuzumab (Herceptin®) is a recombinant humanized monoclonal antibody. Its elimination involves clearance of immunoglobulin (Ig)G through the reticuloendothelial system (as in the case of all monoclonal antibodies). There are no clinical studies in ESRD patients, because they may suffer from a higher incidence of adverse effects (in particular cardiotoxicity). Micallef et al. reported no additional toxicity and good clinical outcome in two HD breast cancer patients treated with trastuzumab administrated 90 min after HD (Micallef et al., 2007). Although fixed doses led to a higher exposure in low body weight subjects, exploratory analyses in patients who underwent s.c. trastuzumab did not show any clinically meaningful association between the incidence of grade ≥3 AEs and exposure, or body weight (Jackisch et al., 2015).

Pertuzumab (Perjeta®) is administered i.v., at a 840 mg loading dose, followed by a 420 mg maintenance dose, every 3 weeks. As with many antibodies, its elimination involves the reticuloendothelial system and it is not excreted through the urine (Perjeta, 2019).

INN-trastuzumab emtasine (T-DM1, Kadcyla, 2019) elimination half-life (approximately 4 days) is shorter than that for a typical IgG1 antibody (i.e. 2–3 weeks); once again, given its high molecular weight, renal function is unlikely to impact clearance.

Lapatinib (Tykerb® or Tyverb®) is administered orally at a dose of 1000–1500 mg/day and is primarily excreted in the feces, less than 2% of administered oral dose being excreted in the urine. Piacentini et al. (2013) reported on a breast cancer patient on HD, in whom the administration of lapatinib was continued for more than 3 years, without any significantly increased toxicity. Another single case of HER2+ breast cancer patient on dialysis has been reported by Sais and Del Barco (2017). While the patient showed gastrointestinal toxicity with diarrhea grade 3 during lapatinib plus capecitabine treatment, the tolerance of trastuzumab and T-DM1 was good. Although PK data are available for ***neratinib*** (Nerlynx®) (Shibata and Chiba, 2015), no cases have been described regarding its use in patients with severe renal dysfunction or on HD.

6. mTOR inhibitors

Two mTOR inhibitors, everolimus (oral administration) and temsirolimus (parental administration), have been registered for oncological indications (Table 5 which includes reccomendation for their dose reduction depending on the severity of kidney impairment). Although ***everolimus*** (Afinitor®) proved to have an antiproliferative effect on glomerular endothelial cells, this effect does not seem to trigger the deterioration of renal function in the long term (Keller et al., 2006). Everolimus is extensively metabolized by the liver via CYP3A4; 80% of the metabolized drug is excreted with the feces, and only 5% in the urine. A PK study of everolimus in 2 HD patients suggested that there is no influence of HD on blood concentration of everolimus (Thiery-Vuillemin et al., 2012).

Some case reports (Donders et al., 2014) along with a retrospective analysis of 11 mRCC patients with ESRD undergoing HD (Guida et al.,

Table 4
General indications (according to EMA and including orphan drug designations) for HER2 inhibitors and dose adjustment recommendations for patients with CKD and on HD.

Monoclonal antibodies		Indication (as monotherapy or in combination)	Dose reduction required?		
			Patients with mild to moderate CKD	Patients with severe CKD	Patients on dialysis
TKIs	Trastuzumab	• Breast cancer • Gastric cancer	No	No data	Limited data
	Pertuzumab	• Breast cancer	No	No data	No data
	INN-TrastuzumabEntamsine (T-DM1)	• Breast cancer	No	No data	Limited data
	Lapatinib	• Breast cancer	No	No data	Limited data
	Neratinib	• Breast cancer	No	No data	No data

CKD, Chronic kidney disease; TKIs, tyrosine kinase inhibitors.

2015) showed that everolimus treatment is feasible, with no unexpected toxicities and good efficacy. It should be highlighted that everolimus proved to be safe and active also in a single patient receiving peritoneal HD, who was started on a reduced dose of everolimus (5 mg daily) due to the choice of the patient's physician.

Temsirolimus (Torisel®) undergoes hepatic metabolism and is mainly excreted via the feces. A PK study showed that there were no significant differences in PK parameters of temsirolimus between patients undergoing HD and those who aren't. Temsirolimus blood concentration was unchanged both immediately before and an hour after HD (Lunardi et al., 2008).

Everolimus and temsirolimus, indeed, are not dialysed by commonly used membranes and do not appear in the dialysate with no influence on their plasma concentration. Unnecessary dose adjustments should, therefore, be avoided (Porta et al., 2015).

Miyake et al. reported 10 Japanese HD patients treated with temsirolimus for mRCC. They observed a good outcome without unexpected severe adverse events, with a relative dose intensity of 89.5% throughout the whole study (Miyake et al., 2013).

7. BCR-ABL inhibitors

BCR-ABL inhibitors are small molecule TKIs endowed with different pharmacologic profiles which are presently approved mainly for hematological malignancies (Table 6, including recommendation for their dose reduction depending on the severity of kidney impairment).

Following mainly hepatic metabolization via CYP3A4 or CYP3A5, ***Imatinib mesylate*** (Glivec®) and its metabolites are eliminated mostly in feces due to hepatobiliary excretion, with 13% of excretion in the urine (Peng et al., 2005). Thus, nephrotoxicity is a relatively rare event. In one study considering patients with chronic myeloid leukemia treated with this drug, AKI and CKD were observed in 7% and 12% of cases, respectively. The main mechanisms of renal damage seems to be related either to toxic tubular damage, or – more realistically – to tumor lysis syndrome.

Patients with mild and moderate renal dysfunction have 1.5- to 2-fold higher plasma exposure than patients with normal renal function, even if the free drug fraction (not binded to alpha-1-acid glycoprotein) is similar regardless of renal function (Glivec, 2019). Gibbons et al. (2008) studied patients with RI showing that daily imatinib doses up to 800 or 600 mg were well tolerated by patients with CrCL 40–59 mL/min and CrCL 20–39 mL/min, respectively, despite having increased imatinib exposure. However, the summary of product characteristics recommends administering 400 mg daily, as a starting dose, in patients with CrCl 20–59, with dose modifications according to tolerability. Once again, caution is recommended in patients with severe impairment due to lack of data (Ramanathan et al., 2008; Judson, 2008).

In HD patients no dose reductions are required since imatinib is not dialyzable. Furthermore, it can be administered either before or after HD (Niikura et al., 2016; Wada et al., 2012; Ozdemir et al., 2006).

Notably enough, a renoprotective effect has also been described for imatinib, which proved able to improve fibrotic and inflammatory markers in murine models of kidney disease (Wang-Rosenke et al., 2013) as well as in few cases of immune-mediated kidney disease (Elmholdt et al., 2013). In a rat model of nephrotoxic serum nephritis, imatinib led to marked renoprotective effects, including suppressed proteinuria and improved renal function. This activity is realistically due to its specific molecular targets with profibrotic activities: ABL1, SCFR, LSK, CSF-1 receptor, and PDGFRs (Buchdunger et al., 2002). Thus, imatinib is a potentially attractive therapeutic option for patients with autoimmune kidney disease, expecially those with a disease requiring chronic suppression of antibody production, as in the case of severe membranous nephropathy, systemic lupus erythematosus, chronic humoral rejection after renal transplantation, and cryoglobulinaemic vasculitis (Wallace and Gewin, 2013; Wallace et al., 2012; Chandran et al., 2009). Furthermore, in a preclinical study, early short-term treatment with imatinib effectively prevented chronic allograft nephropathy after kidney transplantation (Savikko et al., 2011) through

Table 5
General indications (according to EMA and including orphan drug designations) for mTOR inhibitors and dose adjustment recommendations for patients with CKD and on HD.

TKIs		Indication (as monotherapy or in combination)	Dose reduction required?		
			Patients with mild to moderate CKD	Patients with severe CKD	Patients on dialysis
	Temsirolimus	• Kidney cancer • Mantle cell lymphoma	No data	No data	No
	Everolimus	• Kidney cancer • pNET • Lung or gut NET • Breast cancer • SEGA	No	No	No

CKD, Chronic kidney disease; TKIs, tyrosine kinase inhibitors; pNET, pancreatic neuroendocrine tumors; NET, neuroendocrine tumors; SEGA, sub-epndymal giant astrocytomas.

Table 6
General indications (according to EMA and including orphan drug designations) for BCR-ABL inhibitors and dose adjustment recommendations for patients with CKD and on HD.

TKIs	Indication (as monotherapy or in combination)	Dose reduction required?		
		Patients with mild to moderate CKD	Patients with severe CKD	Patients on dialysis
Imatinib	• CML • Ph^+ ALL • MD/MPD • HES/CEL • GIST • Dermatofibrosarcoma protuberans	Mild CDK: no. Moderate CKD: suggested	Suggested	No
Nilotinib	• CML	No	No data	Limited data
Dasatinib	• CML • Ph^+ ALL	No	No data	No data
Bosutinib	• CML	Mild CDK: no. Moderate CKD: limited data	Limited data	No data
Ponatinib	• CML • Ph^+ ALL	No	Limited data	No data
Bafetinib	• CML	No	No data	No data

CKD, Chronic kidney disease; TKIs, tyrosine kinase inhibitors; CML, ChronicMyeloidLeukemia; Ph^+ ALL, Philadelphia-chromosome-poitive Acute LymphoblasticLeukemia; MD/MPD, Myelodysplastic/Myeloproliferativediseases; HES/CEL, HypereosinophilicSyndrome/ChronicEosinophilicLeukaemia; GIST, gastrointestinalstromaltumors.

Table 7
General indications (according to EMA and including orphan drug designations) for CDK4/6 inhibitors and dose adjustment recommendations for patients with CKD and on HD.

TKIs	Indication (as monotherapy or in combination)	Dose reduction required?		
		Patients with mild to moderate CKD	Patients with severe CKD	Patients on dialysis
Palbociclib	• Breast cancer	No	No data	No data
Ribociclib	• Breast cancer	No	No data	No data
Abemaciclib	• Breast cancer	No	No data	No data

CKD, Chronic kidney disease; TKIs, tyrosine kinase inhibitors.

inhibition of PDGFRs and TGF-β1.

Nilotinib (Tasigna®) and ***dasatinib*** (Sprycel®) are second-generation c-ABL inhibitors. Both of them are metabolized by CYP3A4. The renal excretion is absent for nilotib and only 4% for dasatinib. Therefore, a decrease in total body clearance is not expected in patients with RI, although there are few data on the safety and efficacy of these drugs in patients with kidney impairment (Tian et al., 2018; Gnoni et al., 2011). Studies evaluating dasatinib in patients with newly diagnosed or pre-treated CML excluded patients with serum creatinine concentration > 3 and > 1.5 times the upper limit of the normal range, respectively. Clinical studies have not been performed in patients with impaired renal function treated with nilotinib (Tasigna, 2019). Sasaki et al. (2016) suggested that nilotinib and dasatinib are safe and effective therapies for patients affected by chronic myeloid leukemia (CML) with pre-existing renal dysfunction (CrCl 20-59) although associated with a greater risk of reversible AKI.

There are no data for dasatinib, and only few data for use of nilotinib in HD. Three case series of CML patients treated with nilotinib on HD having been reported so far. Plasma concentration of nilotinib were not significantly different before and after HD session, suggesting that the standard dose of this agent can be safely administered in HD patients (Onaka et al., 2012).

Bosutinib (Bosulif®) is very similar to imatinib in terms of activity on renal function. As a matter of fact, long-term bosutinib treatment is associated with an apparently reversible decline in renal function with frequency and characteristics similar to those observed with imatinib (Cortes et al., 2017). Increasing exposure (AUC) in patients with moderate and severe RI during studies was observed (Bosulif, 2019). Other studies, including a randomized, placebo-controlled, trial (Tesar et al., 2017) showed that it can play a positive role on the kidney, being able to ameliorate polycystic kidney disease. Indeed, c-Src inactivation – one of the biological activities of bosutinib – proved able to reduce renal epithelial cell-matrix adhesion, proliferation and cyst formation (Sweeney et al., 2008; Elliot et al., 2011).

No data, on the contrary are available regarding the novel inhibitors ***ponatinib*** (Iclusig®) and ***bafetinib***. Patients with CrCl ≥ 50 mL/min should be able to safely receive iclusig with no dosage adjustment. Caution is recommended when administering Iclusig to patients with CrCl < 50 mL/min, or ESRD.

8. CDK4/6 inhibitors

CDK4/6 inhibitors are highly selective reversible inhibitors of cyclin-dependent kinases (CDK)-4 and -6. General EMA indications for the use of these agents are reported in Table 7, together with recommendations for their dose reduction depending on the severity of kidney impairment.

Palbociclib (Ibrance®) is extensively absorbed, metabolized, and excreted in feces (74.1%), as well as in the urine (17.5%). The urinary and fecal recovery of unaltered palbociclib was 6.9 and 2.3% of the administered dose, respectively (Xiao et al., 2017).

Ribociclib (Kisquali®) is also extensively metabolized by the liver and the kidneys, with the unaltered drug accounting for 17.3% and 12.1% of the dose in feces and urine, respectively. As for its metabolites, they are eliminated mainly through the feces (about 69%), with a smaller (but significant) amount passing through renal route (about 22%) (Curigliano et al., 2017).

Data from PK trials shown that mild and moderate RI didn't effect PK of palbociclib and ribociclib, suggesting no need for drug's dose adjustment in this setting. The PK of palbociclib and ribociclib have not been studied in patients with severe RI or undergoing HD. Minimal unalterated drug is recovered in the urine, suggesting renal failure would not significantly impact drug levels (Xiao et al., 2017).

One study of palbociclib and one study of ribociclib has been

completed in patients and healthy volunteers with different stages of kidney injury, not undergoing HD; results are presently still pending (NCT, 02085538 and NCT, 02431481). Early studies (Pabla et al., 2015; Sprowl et al., 2013) have shown that pharmacological inhibition of CDK4/6 can provide protection from cisplatin-induced AKI and prevent OCT2-mediated toxicities associated with multiple prescription drugs, including platinum-based chemotherapeutics. This interesting discovery surely needs a more thorough insight.

Abemaciclib (Verzenios, 2019) has a prevalent hepatic metabolism that accounts for its main clearance. Renal excretion of abemaciclib is very low, accounting for about 3%. Thus, no dosage adjustment is required for patients with mild or moderate RI (CLcr ≥ 30 mL/min) (Tate et al., 2018). No data exist on the PK of abemaciclib in patients with severe RI (CLcr < 30 mL/min), ESRD, or during HD.

Notably, abemaciclib has been shown to increase serum creatinine due to the inhibition of renal tubular secretion transporters, without affecting glomerular function. For this reason, alternative markers (BUN, cystatin C, or calculated GFR, which are not based on creatinine) should be considered in order to determine whether renal function is impaired (Versenios – EMA).

9. BRAF and MEK inhibitors

BRAF synergize with MEK inhibitors and thus are usually given concomitantly in patients with malignant melanoma and, to a lesser extent also NSCLC harboring BRAF mutations (Table 8, including recommendation for their dose reduction depending on the severity of kidney impairment). In a pharmacokinetic population analysis, mild to moderate renal disfunction did not affect the clearance of ***vemurafenib*** (Zelboraf®), while there is the necessity to exercise caution in patients with severe RI, as data regarding its use are limited, involving just one patient in clinical trials (Flaherty et al., 2011). Similarly, no dose adjustment of ***dabrafenib*** (Tafinlar®) is required for patients with mild or moderate CKD. However, since renal excretion of dabrafenib is higher than that of vemurafenib (23% urinary excretion versus 1%) and the risk of accumulation in patients with severe CKD or ESRD is higher, dabrafenib should be used with greater caution in the setting of kidney impairment (Wanchoo et al., 2016). Despite this, vemurafenib is reported to be more nephrotoxic than dabrafenib. Furthermore, this renal toxicity seems to be more prevalent among male patients with melanoma, and related to tubular interstitial injury (Jhaveri et al., 2015).

As far as the use of BRAF inhibitors in dialysis is concerned, only 2 case reports (one patient treated with vemurafenib monotherapy while on peritoneal dialysis, and one patient treated with dabrafenib plus trametinib) (Iddawela et al., 2013; Park et al., 2017) have been reported, suggesting that the treatment is feasible, although dose reductions are often needed. In particular, in the case of the first patient, vemurafenib had to be reduced due to QTc persistence. Considering the high susceptibility of patients undergoing dialysis to cardiac diseases and electrolyte disturbances, careful monitoring is essential during vemurafenib treatment.

Presently, no data are available regarding the use of the other BRAF inhibitor ***encorafenib*** (Braftovi®) in this setting.

As far as MEK inhibitors are concerned, in a pharmacokinetic study in patients with mild or moderate CKD, kidney failure had no clinically relevant effect on the exposure to ***trametinib*** (Mekinist®). Therefore, no dose adjustment is required for such patients, while no data are available on its use in patients with severe RI, ESRD, or in those undergoing HD (Porta et al., 2015). No significant difference in ***cobimetinib*** (Cotellic®) pharmacokinetics or steady-state exposure was observed between patient subgroups based on different features, including renal function (Han et al., 2015). This is the probable reason why the adjunction of cobimetinib to vemurafenib resulted in a 60% reduction of acute kidney injury (Teuma et al., 2017).

Data available for ***binimetinib*** (Mektovi®) and ***selumetinib*** support similar exposure in the renal failure patients compared to healthy subjects. Furthermore, selumetinib exposure was lower when it was dosed before versus after HD, although individual exposure was variable. Notably, a unique case of glomerulonephritis with renal granulomatous vasculitis has been observed in a melanoma patient treated with encorafenib and binimetinib (Maanaoui et al., 2017).

10. Poly (ADP-ribose) polymerase (PARP) inhibitors

Available PARP inhibitors seem to greatly differ one from the others in terms of pharmacokinetics (Sun et al., 2018), although there appears to be little difference in the clinical effectiveness and toxicity profiles across them (Brown et al., 2016).

As far as their role in the presence of RI, few data are available. Recommendation for their dose reduction depending on the severity of kidney impairment and general EMA indications for their use are reported in Table 9.

Olaparib (Lymparza®) proved able to ameliorate kidney injury in an experimental mice model (Kapoor et al., 2015), while in patients with moderate RI the AUC increased by 44% compared with normal renal function patients. Therefore, for patients with moderate RI the recommended dose of olaparib is 300 mg twice daily. Instead, no starting dose adjustment is required for ***rucaparib*** (Rubraca®) in patients with a CrCl between 30 and 89 mL/min. Patients with a CrCl less than 30 mL/min or who were receiving HD were excluded from clinical trials (Weil and Chen, 2011). Based upon available PK data, rucaparib's steady-state AUC is increased by 15% in patients with mild RI and by 32% in patients with moderate RI (Swisher et al., 2017), while its PK in the case of severe RI and in patients on HD remain unknown. Given the above data, it was hypothesized that the rucaparib's AUC in patients with severe kidney impairment would be approximately double that of

Table 8
General indications (according to EMA and including orphan drug designations) for BRAF and MEK inhibitors inhibitors and dose adjustment recommendations for patients with CKD and on HD.

TKIs (BRAF inhibitors)		Indication (as monotherapy or in combination)	Dose reduction required?		
			Patients with mild to moderate CKD	Patients with severe CKD	Patients on dialysis
	Vemurafenib	• Melanoma	No	Limited data	Limited data
	Dabrafenib	• Melanoma • NSCLC	No	Suggested	Limited data
	Encorafenib	• Melanoma	No	No data	No data
TKIs (MEK inhibitors)					
	Trametinib	• Melanoma • NSCLC	No	No data	No data
	Cobimetinib	• Melanoma	No	No data	No data
	Binimetinib	• Melanoma	No	No	No data
	Selumetinib	• Neurofibromatosis (type 1)	No	No	No

CKD, Chronic kidney disease; TKIs, tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer.

Table 9
General indications (according to EMA and including orphan drug designations) for PARP inhibitors inhibitors and dose adjustment recommendations for patients with CKD and on HD.

PARP inhibitors	Indication (as monotherapy or in combination)	Dose reduction required?		
		Patients with mild to moderate CKD	Patients with severe CKD	Patients on dialysis
Olaparib	• Cancers of the ovary, fallopian tubes and the peritoneum	Mild CDK: no. Moderate CDK: suggested	No data	No data
Rucaparib	• Cancers of the ovary, fallopian tubes and the peritoneum	No	No data	No data
Niraparib	• Cancers of the ovary, fallopian tubes and the peritoneum	No	No data	No data
Talazoparib	• Breast cancer	No	No data	No data
Veliparib	• Ovarian cancer	No	No data	No data

CKD, Chronic kidney disease; PARP, Poly (ADP-ribose) polymerase.

patients with moderate failure. Therefore, it is thus relatively surprising that the only dialysis patient treated to date with rucaparib did receive reduced doses (Harold et al., 2018).

No specific data in this setting are available for the other PARP inhibitors ***niraparib*** (Zejula®), ***talazoparib*** and ***veliparib***.

11. ALK inhibitors

The parental compound *crizotinib* (Xalkori®) is predominantly eliminated in feces (63%) and, at a lesser extent, in urine (22%). PK parameters are known to remain unaltered in the presence of RI, though the drug has not been studied in patients with ESRD. Thus, current recommendations are not to adjust its dose in patients with mild or moderate kidney impairment (Tan et al., 2017), and to reduce dosage from the standard dose of 250 mg twice daily to 250 mg once daily in patients with CrCl < 30 ml/min not requiring dialysis (Izzedine et al.; 2016). Again, no recommendations are available for those with ESRD. No case reports on the use of crizotinib, ceritinib (Zykadia®), alectinib (Alecensa®), brigatinib (Alunbrig®), entrectenib or lorlatinib during dialysis have been reported so far.

Treatment with crizotinib has been associated with kidney failure, an increased risk for the development and progression of renal cysts, the development of peripheral edema, and rare electrolyte disorders (Izzedine et al., 2016). While alectinib has been associated with progressive kidney injury (Nagai et al., 2018), another report demonstrated that it was able to induce the regression of crizotinib-induced complex renal cysts (Taima et al., 2017). Recommendation ALK inhibitors dose reduction depending on the severity of kidney impairment and general EMA indications for their use are reported in Table 10.

12. Discussion

The increasing availability of novel, and more active, biological anticancer agents has greatly improved the outcome of many cancer patients. Unfortunately, data regarding the safety profile of many of these agents in special patient populations (including patients with RI) are still incomplete or totaly unavailable, despite a recent call from regulatory authorities to increase the number of studies dedicated to these patients (EMA Guideline, 2012).

We are witnessing a vicious circle. On one hand, life expectancy of cancer patients is increasing, leading to a higher likelihood of developing some degree of kidney impairment (spontaneous or treatment-induced); on the other hand, patients with kidney impairment, or even on HD, are living longer, with an increased risk of developing concomitant cancer.

Unfortunately, the concomitant presence of these two diseases in a given patient often lead to a nihilistic approach, in terms of denying him/her an active treatment, or of administering an uncorrect dose, with all the deriving consequences (increased toxicities or reduction of efficacy) (Porta et al., 2015).

A correct management of CKD cancer patients or those on HD should take into account the shorter life expectancy of these patients, as well as the impact of cancer treatment on their quality of life.

PK data come usually from population studies and, although the number of these studies in patients with mild to moderate RI is fortunately increasing, data for patients with severe RI or on HD is still lacking. Thus, reports regarding the use of many of these agents in patients on HD remain anecdotal and mainly limited to single case reports or small case series, often lacking any PK insight. Dialyzability and residual renal function, which may indeed impact on PK and thus on the risk of the accumulation of the drug, are often not reported, making most of these reports almost useless.

Given these premises, it is not surprising that the dosage of anticancer treatments in the setting of severe kidney impairment or in HD patients is often empirically managed. In this scenario, unnecessary but quite common dose reductions could be can be either dangerous or uneffective, since a correlation between dose intensity and treatment outcome has been described for many targeted agents (Houk et al., 2010).

Many targeted agents have a minimal renal excretion and can thus

Table 10
General indications (according to EMA and including orphan drug designations) for ALK inhibitors inhibitors and dose adjustment recommendations for patients with CKD and on HD.

ALK inhibitors	Indication (as monotherapy or in combination)	Dose reduction required?		
		Patients with mild to moderate CKD	Patients with severe CKD	Patients on dialysis
Crizotinib	• NSCLC	No	Suggested	No data
Ceritinib	• NSCLC	No	No data	No data
Alectinib	• NSCLC	No	No data	No data
Brigatinib	• NSCLC	No	No data	No data
Entrectenib	• Metastatic solid tumors with NTRK fusion	No	No data	No data
Lorlatinib	• NSCLC	No	No data	No data

CKD, Chronic kidney disease; NSCLC, non-small cell lung cancer.

Box 1
Recommendations on the use of targeted therapy in CKD and HD cancer patients.

PK of new several targeted therapy agents has been extensively reported with minimal or meaningless renal excretion for most of them, providing a fair safety profile to these drugs.
Most targeted agents can be used with the same patterns and the same dosage in mild and moderate RI. The attitude of starting anticancer treatment with a reduced dose, followed by its increase in case of good tolerability, is common but it is not evidence-based and can be detrimental when PK data are available.
Data in severe, end-stage renal disease or HD patients are mostly limited to single case reports and small case series making it difficult to draw scientific supported conclusions.
Although renal toxicity of biological agents can be overcome by HD treatment, the ESRD-related changes (e.g., hypoalbuminemia, edema, metabolic acidosis, abnormal enteric and drug metabolism or reabsorption) can alter the PK profile, increasing the risk of developing other dose-related adverse effects. Caution in these setting is warranted.
Patients with CKD and HD need a complex assessment requiring strong cooperation between oncologist, nephrologist and pharmacist with the aim to provide a complete view of risks, benefits and management of anti-cancer treatment in these populations.
Further prospective clinical investigation in larger cohorts of CKD and HD patients is needed in order to establish evidence-based guidelines.

CKD, Chronic kidney disease; ESRD, end-stage renal disease; HD, hemodialysi; PK, pharmacokinetic.

be used in mild and moderate kidney impairment or during HD without dose adjustments. The attitude of starting anticancer treatment with a reduced dose, followed by its increase in case of good tolerability, is common but it is not evidence-based, and has no sense when adequate PK data are available.

Clinical trials including advanced CKD and HD patients – who are almost often exlcuded from enrolment (Porta et al., 2016) – would be required to define the correct doses and schedules of treatment.

As a whole, a greater cooperation between oncologists, nephrologists and pharmacologists is inevitable in order to select the appropriate treatment for each patient, aiming at improving the likelihood of a clinical benefit, and not just at providing some care.

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.

Conflict of interest statement

The Authors declare no conflict of interests.

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