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Position Paper

International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency

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ABSTRACT

A SIOG taskforce was formed to discuss best clinical practice for elderly cancer patients with renal insufficiency. This manuscript outlines recommended dosing adjustments for cancer drugs in this population according to renal function. Dosing adjustments have been made for drugs in current use which have recommendations in renal insufficiency and the elderly, focusing on drugs which are renally eliminated or are known to be nephrotoxic. Recommendations are based on pharmacokinetic and/or pharmacodynamic data where available. The taskforce recommend that before initiating therapy, some form of geriatric assessment should be conducted that includes evaluation of comorbidities and polypharmacy, hydration status and renal function (using available formulae). Within each drug class, it is sensible to use agents which are less likely to be influenced by renal clearance. Pharmacokinetic and pharmacodynamic data of anticancer agents in the elderly are needed in order to maximise efficacy whilst avoiding unacceptable toxicity.

1. Introduction

Physicians face a special challenge in providing effective cancer chemotherapy for elderly patients. The elderly comprise a rapidly increasing treatment population that have undergone and are undergoing physiological changes associated with ageing, including declining renal function and decreasing reserve in multiple organ systems, which predispose them to unpredictable toxicities of cancer drug treatment. In addition, comorbidities (particularly vascular pathologies) and associated polypharmacy complicate the situation still further. It has been reported that elderly cancer patients take a median of five different prescribed medications, while a quarter also use non-prescription drugs.[1] Polypharmacy can alter absorption by binding drugs in the gastrointestinal tract, changing adsorption or pH, and by competition for binding sites.

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A SIOG taskforce discussed best clinical practice for treating elderly patients with renal insufficiency. This manuscript summarises the consensus recommendations of this taskforce with regards to dosing adjustments for cancer drugs administered to this population.

2. Renal insufficiency

The impact of physiological changes associated with age (for example modifications of renal function, hepatic metabolism, body fluids and muscle/fat repartition) on the pharmacokinetic and pharmacodynamic properties of drugs can be considerable, particularly for the renal elimination of drugs and metabolites. This is especially so for those drugs that are principally renally excreted and/or are nephrotoxic. These drugs typically have a narrow therapeutic range and for patients who present with reduced renal function, careful dose adjustment is indicated to avoid drug accumulation and toxicity. In comparison to younger patients, less is known about the appropriate use of anticancer therapy in the elderly, and treatment decisions in this group remain difficult. Fortunately, interest has increased over the last few years, and the number of publications in this field are rising.[2]

3. Age and age-related performance

For the elderly, there is a need to provide the best cancer treatment possible, whether curative or palliative, whilst avoiding the toxicities of cancer treatment that may be exacerbated by poor renal function or general functional status. Inadequate dosing may compromise efficacy whilst overestimation of renal function may impair safety. There is an ongoing belief that the elderly do not respond to standard treatment and/or cannot tolerate usual doses of cancer drugs. This is despite the fact that there is now good evidence to the contrary.[3–5]

Deciding how aggressive treatment should be when treating cancer in the elderly is an ethical dilemma. Many fit, elderly patients can benefit from aggressive cancer treatments and need not be relegated to palliative or no therapy. They should be offered the optimal treatment based on functional status rather than on chronological age. In order to do this, we need to know about dose adjustment, drug pharmacokinetics and pharmacodynamics, renal function and drug elimination efficiency. Only a minority of elderly patients have been entered onto clinical trials[6] and age is a significant barrier to recruitment.[7] This means that there is limited information available on exactly the population which has the greatest incidence of cancer and generally requires the most comprehensive pre-therapy assessment. European Organisation for Research and Treatment of Cancer (EORTC) trial investigators have concluded that the elderly should be candidates for all phases of clinical trials and should not be excluded on the basis of age.[8] As it is recognised that renal function deteriorates with increasing age, it is important to avoid potential increases in drug toxicity due to decreased renal function. There needs to be a more comprehensive tool for pre-treatment assessment so that potential problems can be predicted and avoided.

4. Renal function in the elderly

Renal function decline is common in the elderly. By the age of 70, renal function may have declined by 40%.[9] This reduction in glomerular filtration rate (GFR) may lead to enhanced toxicity of drugs, particularly those with significant renal excretion, such as cisplatin, carboplatin, topotecan, methotrexate and ifosfamide. Damage to the vasculature or structures of the kidneys and haemolytic uremic syndrome (HUS) may also occur.[10]

The importance of the decline in GFR was first emphasised in a study of dosages based on renal function leading to a higher therapeutic index.[11] The narrow therapeutic index of anticancer drugs presents a clinical dilemma when these drugs are administered to patients with impaired renal function. Cancer drugs have a narrow therapeutic range and dosage is usually based on the maximum tolerated dose to achieve the best efficacy. Chemotherapy-induced toxicities are common and generally manageable but in patients with reduced organ function, they can result in major organ toxicity. These issues are particularly acute for agents cleared by the kidney and for those with established nephrotoxicity. If renal function is impaired and renal clearance reduced, a standard chemotherapy dose will clear more slowly from the body and result in a significantly increased area under the plasma concentration curve (AUC). This may lead to unacceptable toxicity. Thus, in the elderly, before initiating potentially toxic drug therapy, hydration status should be assessed and optimised and renal function evaluated. Ideally, studies to assess dose adjustments need to evaluate the relationship between drug plasma clearance, renal function, and drug-induced toxicity. This is the approach that has been used for carboplatin but few drugs have been studied in such detail. For drugs that are primarily renally excreted, the dose usually needs to be reduced when the estimated GFR falls below 60 mL/min. For most drugs, it would be helpful to have at least some broad guidelines to assist dose adjustment and there is a need for a more comprehensive tool of pre-treatment assessment so that potential problems can be predicted and avoided.

In patients with renal impairment, comprehensive guidelines for dose adjustment exist for very few chemotherapy agents. In addition, few studies focus specifically on renal impairment in the elderly cancer patient and care must be taken in the interpretation of estimated values from other patient groups.

5. Principles of dose adjustment

Patients with a degree of renal impairment are at risk of drug-induced renal toxicity and a higher total drug exposure and overall toxicity due to decreased renal excretion. Both parameters can have implications for drug selection and dosing. Overestimates of GFR in the elderly cancer patient can lead to serious errors in dosing[12] and subsequent deterioration of renal function. SIOG guidelines which discuss the measurement of renal function have also been developed.[13] The nephrotoxicity of drugs used arises in several ways. It may occur because of dehydration secondary to diarrhea or vomiting, or by direct toxicity. This is the case with mitomycin and

pamidronate, for example, which are toxic to the glomerulus; and with cisplatin, methotrexate and zoledronic acid, which are toxic to the tubule. Most often it is considered that drug renal toxicities are additive, especially when the same mechanisms are involved.

There are three methods to adjust dosage according to the degree of renal failure:

- reduce the unitary dose without modifying the administration interval;
- increase the dosing interval without reducing the unitary dose;
- reduce the unitary dose and increase the dosing interval.

Whatever the method used, it is standard practice to stratify patients in GFR ranges to guide adjusted dosing of renally eliminated drugs. Prospectively validated pharmacokinetic and pharmacodynamic trials have evaluated the relationship between carboplatin plasma clearance, renal function and drug-induced toxicity.[14–16] GFR-based dosing of carboplatin is fairly standard, with patients prescribed a dose designed to theoretically achieve a targeted AUC (see below; Refs. 14,15,17). Unfortunately, such studies are rare and few guidelines for dose adjustment of most drugs exist. Summaries of product characteristics (SPCs) or product information do not provide the physician with sufficient information on how to use these drugs in the renally impaired elderly population and there is a clear need for prospectively validated dosing guidelines based on altered renal function.[15]

For all cytotoxic drugs, both toxicity and efficacy are dependent on the plasma drug exposure that corresponds to the AUC. For a particular patient, the AUC is the ratio between dose (bioavailable dose in case of extravascular administration such as oral administration) and the elimination clearance (CL):

AUC = dose/CL for intravenous (IV) administration, and
AUC = F × dose/CL for extravascular administration, where F is bioavailability.

The principle of dose adjustment in elderly patients is therefore to decrease the dose in proportion to the expected decrease in the clearance.

The clearance (or total clearance) of a drug is the sum of the clearances of the eliminating organs, mainly the kidneys and the liver: $CL = CL_{renal} + CL_{hepatic}$.

The hepatic clearance tends to be lower in elderly than in younger patients but that is not the case for every old patient. Moreover, there is no biologic marker to predict the degree of affected liver metabolic capacity. In the absence of strong evidence for liver impairment (such as elevated serum bilirubin or ascites), it is therefore reasonable to hypothesise that the $CL_{hepatic}$ is unchanged in elderly patients.

However, renal function declines with age. Both tubular and glomerular functions are affected. Renal excretion of drugs may be independent of this but it is reasonable to consider that the change in renal excretion may be predicted by evaluating the change in GFR. In standard clinical practice, GFR may be evaluated by estimating the creatinine clearance (CLcr) from serum creatinine (SCr) using an equation. Renal function should be assessed at least by calculation of creatinine clearance in every patient, even when SCr is within the normal range. Many different formulae exist which allow estimation of GFR based on SCr measurement. These include the Jelliffe,[18] Modification of Diet in Renal Disease (MDRD;[19]), Cockcroft-Gault,[20] Wright[21] and Martin formulae.[22] In elderly patients with chronic kidney disease, the abbreviated MDRD (aMDRD) formula should preferentially be used.[12,23] However, the Cockcroft–Gault formula may be more practical for drug dosing purposes in these patients. More details on the optimal method of measuring renal function are explained in another publication from this task force.[13] It is important to note that drug dosing requires the use of a GFR uncorrected for body surface area (BSA).[24] The Jelliffe and MDRD formulae yield a GFR result normalised to 1.73 m^2 BSA, and should thus be adapted for drug dosing to a result in mL/min by using the formula × BSA/1.73. The Cockcroft–Gault, Wright and Martin formulae and the Calvert formula,[15] which is used to calculate carboplatin dose, express GFR in mL/min and do not need correction for BSA.

The dose adjustment for renal impairment can be calculated using the formula:[25]

$$\text{fraction of normal dose} = 1 - f_e \times (1 - k_F)$$

where f_e is the fraction of the original dose excreted as unchanged compound (or active metabolite) within the urine, and k_F is the patient's CLcr/120 mL/min.

In this way, it is possible to propose guidelines for dose adjustment based on CLcr ranges.

The limits of these guidelines are those of the cut-off values since a small change in the CLcr around the cut-off value can be associated with a significant change in dose. If this is the case, it may be better to use the dose adjustment formula above rather than relying on ranges, as a continuous function may be recommended.

The population pharmacokinetic approach uses specific pharmacokinetic studies in order to obtain the relationship between drug clearance and patients' covariates including those already used to estimate CLcr from SCr (i.e. bodyweight, age, gender). By using equations describing the typical values of clearance as a function of these covariates, we may estimate the individual clearance (CL_{ind}) of a particular patient and the adjusted dose would be obtained by multiplying the regular dose by the ratio CL_{ind}/CL_{mean}, where CL_{mean} is the mean clearance of the population treated by the regular dose.

Of the cytotoxic drugs in use, those relying on renal clearance require dose adjustment according to renal function in order to avoid toxicity. Studies to estimate dose adjustment according to renal function have typically used a renal function stratification approach to define dose reductions between established cut-off values of renal clearance. Ideally, there should be a continuous adjustment of dose in line with declining renal function.

5.1. *Drug interactions*

The high incidence of comorbidities in the elderly means that many elderly patients are receiving multiple agents and the influence of polypharmacy on the pharmacokinetics of

anticancer drugs must be considered. The risk for drug–drug interactions increases with the number of medications being taken[26] and studies show that dangerous drug-drug interactions are not uncommon in patients receiving multiple medications.[27]

5.2. *Dose adjustment recommendations: the current situation*

Kintzel and Dorr reviewed 48 anticancer drugs and provided general guidelines for adjusting doses of renally excreted or nephrotoxic drugs in patients who present with altered renal function.[25] Recommendations in this report were based on the documented pharmacokinetic and pharmacodynamic behaviour of antineoplastic agents with respect to their renal elimination and toxicity. In this review, documentation of 30% or greater renal clearance of the active drug or toxic metabolite was considered sufficient to warrant a recommendation for dosage adjustment in renally impaired patients. However, it is recommended that pharmacokinetic and/or pharmacodynamic studies be conducted for every drug in order to safely treat patients with renal insufficiency. It should be appreciated that hepatic metabolism may also be drastically reduced in patients with renal insufficiency due to interactions with uremic toxins, enzymes and transporters. In this study, most of the anticancer agents required no dose adjustment in patients with altered renal function but 12 of the 48 agents reviewed were documented as nephrotoxic and 17 had a renal clearance equal to or exceeding 30% of the administered dose. Dosing adjustments for renal impairment were calculated using the dose adjustment formula described previously and modifications of this formula were provided to adjust the dosage to allow for different circumstances depending on the patient's clinical history and status. For example, one formula was derived from pharmacokinetic studies in paediatric patients and another enables the clinician to predict and modulate thrombocytopenia, the dose-limiting side-effect of carboplatin.

The following list focuses on just some of the drugs in current use which have recommendations for use in renal insufficiency and the elderly. A summary of dosing recommendations is shown in Table 1. Table 2 contains data on the use in renal failure of drugs that have limited renal elimination. Ideally, these dosing guidelines should be adjusted depending on the method of creatinine measurement used. However, this is not possible, as the clinical evidence used to generate these guidelines does not always specify which measurement technique was used.

5.3. *Platinum compounds*

The platin derivatives are the most well-known anticancer drugs in terms of their nephrotoxicity, which is well documented. They do not represent a homogeneous therapeutic class. Oxaliplatin can not be considered as an analogue of cisplatin and carboplatin since their DNA adducts are not recognised by the same DNA repair systems. Moreover, these three drugs are not renally eliminated to the same proportions and their nephrotoxicity differs largely with each other. Nephrotoxicity is the dose-limiting toxicity of cisplatin. However, if the nephrotoxicity of carboplatin and oxaliplatin is limited, the fraction of the dose eliminated renally is substantial for oxaliplatin (around 50%) and large for carboplatin (around 80% in the case of normal renal function).[28] The significant renal excretion of these compounds means that dose individualisation is needed, particularly for carboplatin, in patients with altered renal function.

5.3.1. *Cisplatin*

Despite being a very effective cancer therapy, cisplatin is also very toxic. Dose-related and cumulative renal insufficiency is the major dose-limiting toxicity of cisplatin and renal toxicity has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m^2. It is manifested by elevations in blood urea nitrogen (BUN) and creatinine, serum uric acid and/or a decrease in CLcr. Most cisplatin elimination corresponds to a non renal pathway i.e. protein binding, which is non reversible for cisplatin. Protein-binding should be considered as an elimination process since the bound fraction can not react with DNA. Finally, cisplatin is recovered in urine, but over a long period after administration as urinary excretion requires protein catabolism.[28]

The maximum concentration of the free ultra filterable platinum fraction has been shown to correlate significantly with nephrotoxicity[29] and it may be appropriate to reduce the rate of infusion in the elderly.[30] Upon drug withdrawal, renal insufficiency stabilises or remains indefinitely impaired.[30] Cisplatin administration therefore requires dose adjustments in patients with renal insufficiency (Table 1).

Cisplatin nephrotoxicity is particularly well documented. Progressive and partially irreversible declines in GFR and renal blood flow may develop with each successive treatment course. Because of this, it is necessary to lower its dosage and actively hydrate patients to minimise toxicity side effects.

The critical events related to renal toxicity seem to occur during the first week following cisplatin administration. Protective measures should therefore be applied before, during and immediately after cisplatin infusion. Hydration with isotonic saline beginning several hours before cisplatin infusion and continuous infusion of saline several days after cisplatin administration are routinely used to prevent cisplatin nephrotoxicity.[31]

A regimen consisting of prehydration using 100 mL/hr of normal saline solution for the 12 h prior to the administration of the compound and continuous infusion of saline during and at least 2 days after cisplatin treatment is recommended, without the use of diuretics which may impair renal function instead of preserving it.[31] In one study of 49 women, CLcr was determined before and 6 days after administration of cisplatin together with three renal toxicity prevention protocols. These were 1) 2 litres normal saline solution, 2) 2 litres normal saline solution and furosemide 40 mg, and 3) 2 litres normal saline solution and mannitol 50 mg. The authors observed that CLcr improved and was similarly preserved in the first two groups compared with the mannitol group.[32] In the US, cisplatin is often given on an ambulatory basis with oral hydration at home. There are limited data on the safety of this approach.[33] Efficacious antiemetic drugs should be given concomitantly to avoid dehydration.

Table 1 – Summary of dosage adjustment recommendations for renally cleared anticancer drugs

Agent	% dose excreted in urine	Dose based on patient's CLcr				References
		90–60 mL/min	60–30 mL/min	30–15 mL/min	<15 mL/min and/or haemodialysis[a]	
Alkylating agents						
Carmustine	60–70	No recommendations, due to lack of pharmacokinetic and/or safety data in patients with renal insufficiency. However, care is warranted since a major part is renally excreted. Kintzel and Dorr[25] have generated guidelines on the basis of renal excretion, but not pharmacokinetic data: 80% normal dose for patients with CLcr ⩽60 mL/min, 75% normal dose for patients with CLcr ⩽45 mL/min, and 70% normal dose in patients with CLcr ⩽30 mL/min.				De Vita et al.[92] Levin et al.[93] Oliverio[94] Russo et al.[95]
Ifosfamide	45	Intermittent dose/day: 1.5 to 3 g/m^2; dose/cycle: 5 to 10 g/m^2			Intermittent dose/day: 1.13 to 2.25 g/m^2 dose/cycle: 3.75 to 7.5 g/m^2	Allen & Creaven[96] Bennett et al.[97] Carlson et al.[98] Cerny et al.[99] Creaven et al.[100] Fleming[101] Kerbusch et al.[102] Kurowski et al.[103] Kurowski et al.[104] Nelson et al.[105] Norpoth et al.[106] Wagner[107]
		Continuous dose/day: 5 to 8 g/m^2	Continuous dose/day: 5 to 8 g/m^2	Continuous dose/day: 5 to 8 g/m^2	Continuous dose/day: 3.75 to 6 g/m^2	
Melphalan	30	Oral *Multiple myeloma:* 0.15 to 0.25 mg/kg/day per os for 4 to 7 days	Oral *Multiple myeloma:* 0.11 to 0.19 mg/kg/day per os for 4 to 7 days		Oral *Multiple myeloma:* 0.075 to 0.125 mg/kg/day per os for 4 to 7 days	Carlson et al.[108] Carlson[109] Casserly et al.[110] Cornwell et al.[111] Kergueris et al.[112] Osterborg et al.[113] Tricot et al.[114]
		Ovarian cancer: 0.2 mg/kg/day per os for 5 days	*Ovarian cancer:* 0.15 mg/kg/day for 5 days		*Ovarian cancer:* 0.1 mg/kg/day per os for 5 days	
		Breast cancer: 0.15 mg/kg/day or 6 mg/m^2 per os for 4 to 6 days	*Breast cancer:* 0.11 mg/kg/day or 4.5 mg/m^2 per os for 4 to 6 days		*Breast cancer:* 0.075 mg/kg/day or 3 mg/m^2 per os for 4 to 6 days	
		IV 100 to 200 mg/m^2 or 2.5 to 5.0 mg/kg for 2 or 3 days	IV 75 to 150 mg/m^2 or 1.88 to 3.75 mg/kg for 2 or 3 days		IV 20 to 100 mg/m^2 or 1.25 to 2.5 mg/kg for 2 or 3 days	
Dacarbazine	68	No recommendations, due to lack of pharmacokinetic and/or safety data in patients with renal insufficiency. However, care is warranted since a major part is renally excreted. Kintzel and Dorr[25] have generated guidelines on the basis of renal excretion, but not pharmacokinetic data: 80% normal dose for patients with CLcr ⩽60 mL/min, 75% normal dose for patients with CLcr ⩽45 mL/min, and 70% normal dose in patients with CLcr ⩽30 mL/min.				Fuger et al.[115] Loo et al.[116] Nathanson et al.[117] Samson et al.[118]
Temozolomide	Majority	Pharmacokinetics appear unchanged in patients with mild-moderate renal dysfunction. Patients with severe renal failure should be monitored closely and consideration given to dose modification. Patients >70 years of age appear to be at an increased risk of myelosuppression and should be monitored closely.				Baker et al.[119] Bleehen et al.[120] Britten et al.[121] Brock et al.[122] Hammond et al.[123] Marzolini et al.[124] Newlands et al.[125]

Table 1 – (*continued*)

Agent	% dose excreted in urine	Dose based on patient's CLcr				References
		90–60 mL/min	60–30 mL/min	30–15 mL/min	<15 mL/min and/or haemodialysis[a]	
Platinum agents						
Carboplatin	95	Adjust according to patient using a formula such as the Calvert formula.				Calvert et al.[15] Chatelut et al.[126] Curt et al.[127] Dooley et al.[17] Egorin et al.[16] Elferink et al.[128] English et al.[129] Gaver et al.[130] Harland et al.[131] Himmelstein et al.[132] Koeller et al.[133] Oguri et al.[134] Suzuki et al.[135] Van Warmerdam et al.[44] Yanagawa et al.[136]
Cisplatin	90	50 to 120 mg/m^2 every 3 to 6 weeks	Not recommended, however if unavoidable an appropriate dose should be used: 25 to 60 mg/m^2 every 3 to 6 weeks		Not recommended, however if unavoidable an appropriate dose should be used: 25 mg/m^2 (evidence in haemodialysis patients).	Bennett et al.[97] Bonnem et al.[137] Buice et al.[138] Gorodetsky et al.[139] Hirai et al.[140] Prestayko et al.[141] Ribrag et al.[142] Tomita et al.[143]
Oxaliplatin	54	85 or 100 mg/m^2 every 2 weeks, or 130 mg/m^2 every 3 weeks			Contraindicated	Graham et al.[144] Massari et al.[48] McKeage[145] Pendyala & Creaven[146] Takimoto et al.[50] Takimoto et al.[51]
Antimetabolites						
Fludarabine	60	IV 25 mg/m^2/day	IV 20 mg/m^2/day	IV 15 mg/m^2/day	IV 15 mg/m^2/day	Hersh et al.[147] Knebel et al.[148] Kuo et al.[149] Lichtman et al.[55] Rosenstock et al.[150]
Methotrexate	55–88	Oral 15 to 30 mg/m^2	Oral 12 to 24 mg/m^2	Oral 7.5 to 24 mg/m^2	Contraindicated	Bennett et al.[97] Bleyer[151] Bostrom et al.[152]
		IM, IV, SC Solid tumours: 30 to 50 mg/m^2	IM, IV, SC Solid tumours: 24 to 40 mg/m^2	IM, IV, SC Solid tumours: 15 to 25 mg/m^2	Contraindicated	Calvert et al.[153] Creinin & Krohn[154] Djerassi et al.[155]
		IA 25 to 50 mg/24 h	IA 20 to 40 mg/24 h	IA 12 to 25 mg/24 h	Contraindicated	Freeman-Narrod et al.[156]
		IR 10 to 15 mg/m^2	IR 10 to 15 mg/m^2	IR 10 to 15 mg/m^2	Contraindicated	Huffman et al.[157] Liegler et al.[158] Shapiro et al.[159] Shen & Azarnoff[160] Teresi et al.[161] Wall et al.[162]

Table 1 – (*continued*)

Agent	% dose excreted in urine	Dose based on patient's CLcr				References
		90–60 mL/min	60–30 mL/min	30–15 mL/min	<15 mL/min and/or haemodialysis[a]	
Capecitabine	95.5	1250 mg/m^2 every 12 h	950 mg/m^2 every 12 h	Contraindicated	Contraindicated	Bajetta et al.[163] Frings[164] Poole et al.[63] Walko & Lindley[165]
Cytarabine	90–96	Normal dose An initial dose 100 mg/m^2/day for 7 to 10 days, or 200 mg/m^2/day for 5 to 10 days followed by 20 mg/m^2/day for 5 to 10 days. High dose 2 to 3 g/m^2 every 12 h	High dose 1 to 2 g/m^2 every 12 h	High dose 1 g/m^2 every 12 to 24 h	High dose 1 g/m^2 every 24 h	Bennett et al.[97] Damon et al.[166] Hande et al.[167] Hasle[168] Smith et al.[169] Van Prooijen et al.[170]
Hydroxyurea	80	2.5 to 25 mg/kg depending on the indication				Belt et al.[171] Bennett et al.[172] Gwilt et al.[173] Newman et al.[174] Rodriguez et al.[64] Yan et al.[175]
Raltitrexed	40–50	60–60 mL/min: 3 mg/m^2 every 3 weeks; 65–55 mL/min: 2.25 mg/m^2 every 4 weeks; 54–25 mL/min: 1.5 mg/m^2 every 4 weeks; <25 mL/min and haemodialysis: contraindicated				Beale et al.[176] Judson et al.[177] Judson[178] Smith et al.[179]
Pemetrexed	70–90	500 mg/m^2 by single IV infusion over 10 min	60–45 mL/min: 500 mg/m^2 by single IV infusion over 10 min <45 mL/min and haemodialysis: contraindicated			Norman[180] Ouellet et al.[181] Mita et al.[65]
Topoisomerase inhibitors						
Etoposide	40–60	Oral 80 to 300 mg/m^2/day for 3 to 5 days, followed by 50 to 100 mg/m^2/day	Oral 60 to 225 mg/m^2/day for 3 to 5 days, followed by 37.5 to 75 mg/m^2/day		Oral 40 to 150 mg/m^2/day for 3 to 5 days, followed by 25 to 50 mg/m^2/day	Bennett et al.[97] Chabot et al.[182] de Jong et al.[183] Hande et al.[167] Higa et al.[184] Inoue et al.[185]
		IV 50 to 150 mg/m^2/day for 1 to 3 days Intensive dosing: 40 to 50 mg/kg	IV 37.5 to 112.5 mg/m^2/day for 1 to 3 days Intensive dosing: 30 to 45 mg/kg		IV 25 to 75 mg/m^2/day for 1 to 3 days Intensive dosing: 20 to 30 mg/kg	Kamizuru et al.[186] Pfluger et al.[187] Pfluger et al.[188] Slevin et al.[189] Watanabe et al.[190]
Topotecan	20–60	1.5 mg/m^2/day	60–40 mL/min: 1.5 mg/m^2/day; 39–20 mL/min: 0.75 mg/m^2/day; <20 mL/min and haemodialysis: not available			Anastasia[191] Grochow et al.[192] Haas et al.[193] Herben et al.[194] Herrington et al.[195] Iacono et al.[196] O'Dwyer et al.[197] O'Reilly et al.[73] Seiter[198] Van Warmerdam et al.[199] Van Warmerdam et al.[200]
Miscellaneous						
Bleomycin	50–70	10 to 20 mg/m^2	7.5 to 15 mg/m^2	7.5 to 15 mg/m^2	5 to 10 mg/m^2	Alberts et al.[201] Bennett et al.[97] Crooke et al.[202] Crooke et al.[203] Hall et al.[204] Harvey et al.[205] McLeod et al.[206] Oken et al.[207] Simpson et al.[208]

Table 1 – (continued)

Agent	% dose excreted in urine	Dose based on patient's CLcr				References
		90–60 mL/min	60–30 mL/min	30–15 mL/min	<15 mL/min and/or haemodialysis[a]	
Bisphosphonates						
Ibandronate	50–60	6 mg every 3 to 4 weeks	6 mg every 3 to 4 weeks	6 mg every 3 to 4 weeks	2 mg every 3 to 4 weeks	Adami et al.[209] Bergner et al.[210] Geng et al.[211] Heidenreich et al.[212] Musso et al.[213]
Pamidronate	20–55	90 mg every 4 weeks	90 mg every 4 weeks	Not recommended	Not recommended	Berenson et al.[214] Davenport et al.[215] Machado et al.[216] Monney et al.[217] Phanish et al.[218] Torregrosa et al.[219]
Zoledronic acid	39	4 mg every 3 to 4 weeks	60–50 mL/min: 3.5 mg every 3 to 4 weeks 50–40 mL/min: 3.3 mg every 3 to 4 weeks 40–30 mL/min: 3 mg every 3 to 4 weeks	Not recommended	Not recommended	Balla et al.[220] Chang et al.[81] Munier et al.[221] Skerjanec et al.[222]

[*] Because drug can be dialysed it should be administered after dialysis.
I = intermittent dosing; C = continuous dosing; IV = intravenous; IM = intramuscular; SC = subcutaneous; IA = intra-arterial; IR = intraruminal.

At present, it is not recommended to administer platinum compounds to patients before objective evidence of euvolemia is present. Further, the platinum should be administered slowly in conjunction with a saline solution infusion that produces a brisk diuresis. Urine flow should be maintained at 3 to 4 L/24 h for the next 2 to 3 days.

5.3.2. *Carboplatin*

Patients with renal insufficiency who cannot tolerate cisplatin may be given carboplatin instead (e.g. bladder cancer patients[27,34–38]). Carboplatin has proven activity against a range of cancers and has the advantage of being much less nephrotoxic, neurotoxic and emetogenic than cisplatin, which it has replaced in many regimens.[39,40] The combination of paclitaxel and carboplatin has been used as an effective treatment for elderly cancer patients with renal insufficiency.[41,42]

About 95% of the drug is excreted by the kidneys, and the development of specific formulas based on GFR and the targeted AUC has permitted the individualisation of the carboplatin dose for maximum effect with tolerable adverse effects (Table 1).

5.3.3. *Prediction of carboplatin clearance*

The reference method to predict carboplatin clearance is based on the Calvert equation:[15]

$$\text{CL (mL/min)} = \text{GFR} + 25 \text{ mL/min}$$

where GFR is the glomerular filtration rate determined by the isotopic ^{51} Cr-EDTA method.

Since determination of ^{51} Cr-EDTA clearance can not be performed in routine practice, CLcr estimated by the Cockcroft-Gault or the Jelliffe equation is often substituted to GFR in the Calvert equation. In order to decrease the impact of the differences between estimated CLcr and GFR, a specific equation was developed by Chatelut et al. by analysing carboplatin data using a population pharmacokinetic approach, for estimating carboplatin clearance:[14]

$$\text{CL} = 0.134 \times \text{BW} + 218 \times \text{BW}(1 - 0.00457 \times \text{age}) \times (1 - 0.314 \times \text{sex})/\text{SCr}$$

with bodyweight (BW) in kg, age in years, sex = 0 if male, = 1 if female, and SCr in μmol/L. For obese patients, mean value between actual and ideal bodyweight should be used.[43]

Several teams compared the respective performance of the different methods proposed to predict carboplatin clearance. Significant bias was observed with the Calvert formula using the Cockcroft-Gault equation, but the Chatelut formula was found to have no significant bias and was precise.[44] However, others reported an over prediction of the carboplatin clearance with the latter formula.[45] These conflicting results may be explained by the diversity of the assays used for SCr measurement.

Recently, a method based on determination of plasma cystatin C has been proposed that incorporates both cystatin C and creatinine plasma levels (together with body weight, age, and gender) in the prediction equation.[46] Carboplatin clearance prediction was found to be superior to the equation based only on SCr. Moreover, the assay has improved precision

and reduced inter-assay variability compared with SCr assays. The equation for carboplatin clearance prediction was:
CL (mL/min) = 110. $[(SCr/75)^{-0.512}]$. $[(cystatinC/1.0)^{-0.327}]$. $[(BW/65)^{0.474}]$. $[(age/56)^{-0.387}]$. $[0.854^{sex}]$, with SCr in μmol/L, cystatinC in mg/L, BW in kg, age in years and sex = 0 if male, = 1 if female. During this work, a non-compensated kinetic Jaffé method was used for SCr determination, but the impact of the SCr assay is limited in comparison with other formulas since contribution of SCr in the prediction is itself limited thanks to the consideration of cystatin C.

Such an approach, which integrates cystatin C and plasma creatinine levels, is preferred. However, as cystatinC is not yet a widely available assay, CLcr estimation by aMDRD and the use of Calvert is reasonable.

5.3.4. *Target AUC*

A pioneer study was carried out by Egorin et al. proposing individualised dose according to both the measured CLcr (pharmacokinetics) and the expected decrease of platelet count (pharmacodynamics).[16] The equation may be used only if carboplatin is administered as monotherapy since combined cytotoxic(s) would increase its haematotoxicity. However, there is some evidence to suggest that there is less thrombocytopenia when paclitaxel is also administered.[47]

The concept of target AUC is widely used to calculate the dose:

$$\text{dose (mg)} = \text{CL}_{\text{predicted}} \times \text{AUC}_{\text{target}}$$

Calculation of the AUC value is somewhat empirical but experience has shown that certain criteria can be applied: higher values of AUC can be targeted when carboplatin is used in combination with paclitaxel compared to other combinations such as carboplatin-cyclophosphamide, -etoposide or -5-fluorouracil.[47] Patients extensively pre-treated with chemotherapy should be treated with a lower AUC value (e.g. for carboplatin-paclitaxel: 6.0–7.5 and 5.0 mg/mL × min for patients not pre-treated and extensively pre-treated, respectively).

5.3.5. *Oxaliplatin*

Oxaliplatin is an approved agent with clinical activity in the treatment of advanced colorectal cancer. About 54% is excreted renally and drug clearance decreases with age.[28,48] The AUC of the free fraction correlates with CLcr. Two small studies of patients treated with the same dose (130 mg/m^2 as monotherapy) of oxaliplatin showed no significant increase in toxicity in the moderately impaired (CLcr range 27–57 mL/min; $n = 10$) compared to the normal (CLcr range 63–136 mL/min; $n = 13$) renal function group.[49] However, a strong negative correlation was observed between CLcr (calculated using the Cockcroft-Gault formula) and free drug plasma availability.[50,51] Since renal impairment entails a longer exposure to platinum in the plasma, oxaliplatin is contraindicated in patients with CLcr <15 mL/min (Table 1;[28]).

5.4. *Antimetabolites*

5.4.1. *Methotrexate*

Methotrexate is widely used in oncology. Direct methotrexate renal toxicity is rare and has only been associated with high dose regimens. Increased toxicity has also been observed in patients receiving low-dose, long-term methotrexate.[52] Excretion is almost entirely by the renal route and is inhibited by NSAIDs, cephalosporins and several other drugs. The methotrexate half-life and clearance has been shown to be significantly prolonged in older patients[52,53] and the dose should be adjusted in the elderly population according to renal function (see Table 1). An alternative dosing formula has been proposed: adjusted dose = normal dose × CLcr/70.[11]

5.4.2. *Fludarabine*

Fludarabine is approved for chronic lymphocytic leukaemia and may be helpful in controlling symptoms in elderly patients with progressive or refractory forms of the disease. It is converted to 2-fluoro-ara-A within minutes of administration and about 23% of the dose is excreted in this form, with an elimination half-life of 6.9–12.4 h. A prolonged half-life of up to 23.9 h has been reported in patients with renal impairment and the severity of fludarabine-related neutropenia is related directly to total body clearance, AUC and half-life.[54,55] Dose adjustments for patients with renal insufficiency have been suggested (Table 1).

5.4.3. *Cytarabine*

Cytarabine is rapidly metabolised in the liver to inactive metabolites and 90–96% is excreted in the urine.[28] Due to increase neurotoxicity in patients with renal insufficiency, dose adjustments are required for high dose therapy (Table 1).

5.4.4. *Gemcitabine*

Gemcitabine has a broad spectrum of action in many cancers and is a useful agent for treating cancers in the elderly. It is metabolised in the liver to the inactive uracil metabolite which is primarily excreted renally. Its renal tolerance has been reported to be good.[56] In patients with existing renal dysfunction, some increased toxicity is seen; however, no dose-adjustments are necessary.[28,57] Reports of gemcitabine-related haemolytic uremic syndrome have caused concern [58–61] and combining gemcitabine with other agents, such as cisplatin, may be problematic for some elderly patients (Table 2).

5.4.5. *Fluorouracil*

Fluorouracil is in common use for a range of cancers. It is metabolised in the liver by dihydropyrimidine dehydrogenase (DPD). At most, 15–20% of the drug is renally excreted. Some authors have suggested a dose reduction of 80% in severe renal failure, but this is not evidence-based.[62] Major decreased DPD activity (e.g. in liver failure) can increase unchanged fluorouracil renal excretion by up to 80–90% and so patients with combined liver and renal impairment may be at increased toxicity risk.

5.4.6. *Capecitabine*

Capecitabine is an oral prodrug of the cytotoxic moiety fluorouracil (5-fluorouracil; 5-FU) that has been developed to increase the therapeutic index and improve convenience and flexibility of administration. It has activity in breast and colorectal cancer and has also been shown to be effective in elderly bladder cancer patients. It is extensively metabolised

in the liver and 95.5% of the dose is excreted renally.[28] Studies specifically investigating the effect of renal function clearly demonstrated toxicity with renal impairment and dose adjustments are therefore indicated on the basis of renal function rather than age (Table 1[63]).

5.4.7. *Hydroxyurea (hydroxycarbamide)*

Hydroxyurea is subject to hepatic metabolism and 80% is excreted in the urine. Dose adjustments should be performed for reasons of tolerance and clinical efficacy (Table 1[28,64]).

5.4.8. *Pemetrexed*

Pemetrexed is primarily excreted unchanged in the urine (70 to 90% in the first 24 h). It is contraindicated in patients with CLcr < 45 mL/min (Table 1). A recent study investigated the toxicities, pharmacokinetics, and recommended doses of pemetrexed in patients with normal and impaired renal function.[65] In patients with impaired renal function pemetrexed plasma clearance positively correlated with GFR, which resulted in increased drug exposures. Pemetrexed 600 mg/m^{2}was well-tolerated (with vitamin supplementation) in patients with GFR $\geqslant$80 mL/min. In patients with GFR 40–79 mL/min, a dose of 500 mg/m^2 along with vitamin supplementation was tolerated.[65] Further studies are needed to determine dosing in renally impaired patients.

5.5. *Alkylating agents*

5.5.1. *Ifosfamide*

Ifosfamide is extensively metabolised in the liver and approximately 5% is excreted unchanged in the urine.[28] The metabolites are also excreted by the kidney and have a longer half-life in the elderly. Renal impairment has been reported with high dose ifosfamide in breast cancer patients[66] and dose reductions according to renal function should be performed (Table 1). The use of protracted infusion regimens or fractionated dosage can improve the therapeutic index and reduce toxicity and may be considered in patients with renal impairment.[67]

5.5.2. *Melphalan*

Melphalan is partly excreted renally and dose adjustment recommendations have been made mainly due to pharmacodynamic reasons (Table 1). High doses of melphalan (200 mg/m^2) have been shown to be poorly tolerated in patients with renal failure.[68,69]

5.5.3. *Dacarbazine*

Dacarbazine is metabolised extensively in the liver and 50% is excreted unchanged in the urine and 18% is excreted as metabolites.[28] No recommendations can be made due to lack of pharmacokinetic and/or safety data (Table 1).

5.6. *Topoisomerase inhibitors*

5.6.1. *Etoposide*

Considerable interpatient variation in pharmacokinetic parameters and therefore drug toxicity occurs with both oral and IV use of etoposide. About 40–60% of the drug is excreted renally[28] and the AUC and haematological toxicity is increased in patients with renal impairment. A 30% dose reduction is recommended when the plasma creatinine level exceeds 1.4 mg/dL[70] and more detailed dose adjustment recommendations are based on the degree of renal impairment (Table 1[25,28,71,72]).

5.6.2. *Topotecan*

Topotecan is routinely used in ovarian carcinoma and 20–60% of the drug is excreted renally. The dose-limiting toxicities are myelosuppression and diarrhea and these correlate closely with the AUC of topotecan. Several equations have been proposed to predict topotecan clearance in patients according to their renal status.[73–75] Dose adjustments are required in moderate, but not mild renal impairment (see Table 1[28,76]).

Cystatin C has been proposed as an alternative endogenous marker of glomerular filtration. Studies indicate that this may be a better marker for renal elimination of topotecan than SCr and CLcr.[77,78]

5.7. *Bisphosphonates*

5.7.1. *Zoledronic acid*

Zoledronic acid is administered intravenously and its effect on renal function is a poorly characterised complication of treatment. It is primarily excreted unchanged via the kidneys.[79]

The standard recommended dose is a 15 min IV infusion (4 mg) monthly. Several studies have observed renal failure with zoledronic acid at this dose.[80,81] The close temporal relationship between drug administration and the onset of renal failure and the partial recovery of renal function following drug withdrawal strongly implicate it in the development of acute tubular necrosis.

Preliminary results from a retrospective analysis of zoledronic acid use in 293 patients with a range of malignancies across all ages concluded that renal dysfunction (measured by increased SCr level) occurs in all age groups but that it seemed to be more common in patients exposed to more than one bisphosphonate and in the elderly (>80 years).[82] Other age-related analysis of zoledronic acid use in phase III clinical trials, however, indicates that although creatinine levels were significantly higher in zoledronic acid treated patients compared with pamidronate, there was no significant difference in renal function between the elderly group (>70 years) and the rest of the patient group ($\leqslant$70 years).[83]

Pre-existing renal insufficiency and multiple cycles of zoledronic acid and other bisphosphonates seem to be risk factors for subsequent renal deterioration with zoledronic acid. Furthermore, a retrospective analysis of hormone-refractory prostate cancer patients with bone metastases receiving zoledronic acid showed that, among the 122 patients identified (mean age at initiation of therapy 70.1 years), the incidence of renal deterioration with zoledronic acid was 24% with 21% necessitating zoledronic acid withdrawal. In this analysis, main risk factors were pre-existing renal insufficiency (RR 4.6), hypercalcemia (RR 4.0) and increasing age (RR 1.1 per additional year).[84]

Other factors such as dehydration or use of concomitant nephrotoxic drugs that both predispose patients to renal

Table 2 – Recommendations for anticancer drugs with limited renal excretion

Agent	% of dose excreted in urine	Use in severe renal failure (<30 mL/min)?	Remarks	References
Alkylating agents				
Chlorambucil	<1	Yes	No adjustment required, but monitor carefully as patients with renal failure are at increased risk of myelosuppression.	Launay-Vacher et al.[28]
Antimetabolites				
Gemcitabine	<10	Caution is warranted	Patients with increased SCr levels greater than 1.6 mg/dL are more sensitive to gemcitabine and are especially prone to skin toxicity and renal failure, but the lack of a correlation between pharmacokinetic parameters and toxicity has made it impossible to provide any specific dose recommendations.	Launay-Vacher et al.[28]
Fluorouracil	10	Caution is warranted	In general no dose adjustment is required. However, in patients with combined hepatic and renal failure great care is warranted.	Young et al.[62] Wildiers et al.[223]
Antimicrotubule Agents *Vinca Alkaloids*				
Vincristine	10–20	Yes	No dose adjustment necessary.	Launay-Vacher et al.[28]
Vinblastine	<1	Yes	Few data available, but assumed similar to vincristine. Toxicity may be increased in the elderly, therefore use with caution.	Launay-Vacher et al.[28]
Vinorelbine	Minority	Caution is warranted	More neutropenia in end-stage renal disease on haemodialytic treatment. However, no pharmacokinetic data are available and there is no evidence that the dose of vinorelbine requires modification in case of renal dysfunction or the elderly.	Khayat et al.[224] Rahmani et al.[225] Rollino et al.[226]
Taxanes				
Paclitaxel	1.3–12.6	Yes	Preclinical studies suggest renal failure, as well as hepatic failure, could modify the pharmacokinetics of paclitaxel. Several case reports/small studies show that treatment with full dose paclitaxel (with or without carboplatin) is feasible in patients with severe renal failure, in patients requiring haemodialysis, and in elderly patients with renal failure. No dose adjustment needed in elderly patients.	Jiko et al.[227] Mori et al.[228] Bekele et al.[229] Furuya et al.[230] Watanabe et al.[231] Tomita et al.[143] Jeyabalan et al.[232] Yang et al.[233] Dreicer et al.[234]
ABI 007	Minor	Yes	–	Sparreboom et al.[235]
Docetaxel	6	Yes	Efficacy and toxicity in patients with metastatic urothelial carcinoma and impaired renal function comparable with the known effects of docetaxel in patients without renal impairment. Patients >60 years may have increased toxicity when docetaxel is used in combination with capecitabine.	Dimopoulos et al.[236]
Topoisomerase inhibitors				
Irinotecan	<20	No data	Age >70 years independently predicted the occurrence of grade 3/4 diarrhea. Treatment with the every-3-week schedule was associated with a lower rate of grade 3/4 diarrhea. Delayed diarrhea was increased in patients with advanced age. It is recommended that patients >70 years, with prior pelvic irradiation, or poor performance status start at reduced doses (e.g. in monotherapy 300 mg/m^2 instead of 350). Modest changes in renal function do not appear to affect irinotecan plasma concentration.	Fuchs et al.[237] Rougier et al.[238]

Table 2 – (continued)

Agent	% of dose excreted in urine	Use in severe renal failure (<30 mL/min)?	Remarks	References
Antitumor Antibiotics				
Doxorubicin	10	Caution is warranted	There are no guidelines available for dose adjustment in renal impairment, but pharmacokinetic studies in haemodialysis patients show a greater exposure to doxorubicin in haemodialysis patients compared to non-haemodialysis patients. On the other hand, doxorubicin-containing regimens have been frequently used in patients with moderate-to-severe renal dysfunction, e.g. in multiple myeloma or non-Hodgkin's lymphoma, and no specific problems have been reported.	Speth et al.[239] Yoshida et al.[240] Pandit et al.[241] Choi et al.[242]
Liposomal doxorubicin	5	No data	Population pharmacokinetic data (in the range of CLcr tested of 30–156 mL/min) demonstrate that clearance is not influenced by renal function. However, no pharmacokinetic data are available in patients with CLcr of less than 30 mL/min. Furthermore, there is limited information in patients > 60 years.	Gabizon et al.[243]
Epirubicin	9	Caution is warranted	In principle no problem, but in severe renal failure, clearance might become elevated. However, no dose reduction guidelines have been established for these patients or in the elderly.	Camaggi et al.[244]
Daunorubicin	<25	No data	Reduce dose to 50% if creatinine greater than twice upper limit of normal. Use should be avoided in patients 75 years of age.	Launay-Vacher et al.[28]
Mitoxantrone	<11	Yes	No dose adjustment necessary.	Alberts et al.[245]
Mitomycin	<10	Yes	Mitomycin can induce renal failure, often associated with microangiopathic haemolytic anemia. Of particular interest is the fact that the onset of renal dysfunction followed by mitomycin administration occurs by an average after 10 to 11 months. However, because renal impairment does not alter mitomycin pharmacokinetics, and renal excretion is not a major route of elimination, it is suggested that renal impairment does not call for dose adjustment.	Hamner et al.[246] Verweij et al.[247]
Idarubicin	<6.6	Caution is warranted	The total plasma clearance of both idarubicin and idarubicinol is reduced significantly in renal impairment, implying that dose adjustments are required: 50% for SCr >200μmol/L (>2.3 mg/dL) 75% for SCr >177μmol/L (>2.0 mg/dL).	Furuya et al.[230] Robert[248] Buckley et al.[249]
Hormonal therapies				
Tamoxifen	<1	Yes	No dose adjustment necessary.	Sutherland et al.[250]
Bicalutamide	Minor	Yes	No dose adjustment necessary.	Tyrrell et al.[251] Cockshott[252]

Table 2 – (continued)

Agent	% of dose excreted in urine	Use in severe renal failure (<30 mL/min)?	Remarks	References
Other agents				
Thalidomide	0.7	Caution is warranted	In patients with severe renal failure or haemodialysis, thalidomide can be safely administered with comparable efficacy and toxicity as in patients with normal renal function. Although clearance during dialysis is doubled, thalidomide dose need not be changed for patients with decreased kidney function. However, clinicians must be aware of the risk of severe thalidomide-associated hyperkalemia, especially in haemodialysed patients. Thalidomide can also potentiate nephrotoxicity of aminoglycoside antibiotics in patients with multiple myeloma.	Tosi et al.[253] Eriksson et al.[254] Fakhouri et al.[255] Montagut et al.[256]
Bortezomib	Minor	Few data	Its use seems safe in patients with impaired renal function, although experience is limited.	Jagannath et al.[257]
Anti-VEGF antibodies	–	No data	Among the patients treated with bevacizumab, 22% developed hypertension necessitating treatment and 26.5% had proteinuria. No patient developed renal failure and 6 patients out of 76 presented microscopic haematuria. To date, due to the lack of data, no recommendations exist on anti-VEGF antibodies dose adjustment in patients with renal insufficiency.	Hurwitz et al.[258]

deterioration should be identified and managed. Renal monitoring guidelines in the prescribing information for zoledronic acid recommend that SCr be measured before each dose is given and suggest that treatment is withheld or not initiated in patients with severe renal deterioration (CLcr <30 mL/min).

For patients with mild to moderate renal impairment, dose adjustment is necessary during or before initiating zoledronic acid therapy and is calculated from renal function (Table 1).

5.7.2. *Pamidronate*

Like zoledronic acid, conflicting reports for renal safety with pamidronate use are available. Deterioration of renal function (including renal failure) has been reported following long-term treatment in patients with multiple myeloma.[85] However, another study of long-term pamidronate treatment in patients with breast or prostate cancer or multiple myeloma indicated that treatment was generally well tolerated.[86] Only two cases of acute renal insufficiency occurred and this was reversible and without consequence.

Renal function monitoring is recommended prior to each dose and treatment should be withheld if there is evidence of deterioration. Guidelines for dose reduction according to renal function are presented in Table 1.

5.7.3. *Ibandronate*

In contrast to the other bisphosphonates in common use, ibandronate has a favourable safety profile.

Data from an elderly patient (⩾65 years) subset analysis of phase III trials, showed that ibandronate has a renal safety profile comparable to placebo. This is consistent with the published analysis of the total study population;[87,88] neither treatment group showing renal function deterioration over the 96 week study period.[83]

In a study of urologic cancer patients, renal function assessed by measuring SCr levels was constant over 28 days following and intensive IV loading-dose schedule (6 mg infused over 1 h on 3 consecutive days) in patients with compensated renal insufficiency at baseline; no adverse renal events were reported.[89,90]

Dosage recommendations state that no dosage adjustment is necessary for patients with mild or moderate renal impairment where CLcr is ⩾30 mL/min, and only below 30 mL/min CLcr, the dose should be reduced (see Table 1).

Approved product labelling for ibandronate in the European Union recommends monitoring renal function only according to clinical assessment of each patient at the discretion of the physician and there are no dosing restrictions for ibandronate in patients who also are receiving cancer therapies with nephrotoxic side effects.

Because renal toxicity is not a concern with oral ibandronate,[91] this is a viable alternative to IV treatment for elderly patients who have left hospital.

6. Conclusions

Cancer treatment in the elderly is an individualised process that requires careful assessment of each patient prior to therapy initiation to achieve dose optimisation. Renal function should be assessed at least by calculation of CLcr in every pa-

tient, by aMDRD or Cockcroft-Gault formulae, even when serum creatinine is within the normal range.

Dose escalations can then be made at a later stage, if tolerability allows. Before initiating drug therapy, some sort of geriatric assessment should be conducted that considers comorbidities and polypharmacy, hydration status and renal function.

Despite the individuality of physiological status in the elderly, the general trend of reducing renal function with age indicates that, within each drug class, it is sensible to use agents which are less likely to be influenced by renal clearance, or for which appropriate methods of prevention for renal toxicity exist. Furthermore, co-administration of known nephrotoxic drugs such as NSAIDS or Cox-2 inhibitors should be avoided or minimised.

In general, age is not a contraindication to full-dose chemotherapy for most drugs. The main limiting factors are poor functional status and comorbidity. There is a pressing need for clinical trials that are designed to evaluate the contribution of renal function to efficacy and toxicity in the elderly. Data on the pharmacokinetic and pharmacodynamic properties of anticancer agents in the elderly will help to establish appropriate therapy regimens that maximise efficacy whilst avoiding unacceptable toxicity.

Conflict of interest statement

None declared.

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