Initiation and termination of dialysis in older patients with advanced cancer: providing guidance in a complicated situation

Ben Sprangers, Annelien Van der Veen, Marije E Hamaker, Siri Rostoft, Sheron Latcha, Stuart M Lichtman, Bart de Moor, Hans Wildiers

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Department of Microbiology, Immunology and Transplantation, Laboratory of Molecular Immunology, Rega Institute (Prof B Sprangers PhD) **and Department of Oncology** (Prof H Wildiers PhD), **KU Leuven, Leuven, Belgium; Division of Nephrology, Department of Internal Medicine** (Prof B Sprangers, A Van der Veen) **and Department of General Medical Oncology** (Prof H Wildiers), **University Hospitals Leuven, Leuven, Belgium; Department of Geriatric Medicine, Diakonessenhuis Utrecht, Netherlands** (M E Hamaker PhD); **Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway** (Prof S Rostoft PhD); **Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway** (Prof S Rostoft); **Renal Division** (S Latcha MD), **Department of Medicine** (Prof S M Lichtman MD), **Memorial Sloan Kettering Cancer Center, New York, NY, USA; Division of Nephrology, Jessa Ziekenhuis, Hasselt, Belgium** (B de Moor MD); **Faculty of Medicine and Life Sciences, University of Hasselt, Diepenbeek, Belgium** (B de Moor)

Correspondence to:
Prof Ben Sprangers, Division of Nephrology, Department of Internal Medicine, University Hospitals Leuven, b-3000 Leuven, Belgium
ben.sprangers@uzleuven.be

Cancer and chronic kidney disease prevalence both increase with age. As a consequence, physicians are more frequently encountering older people with cancer who need dialysis, or patients on dialysis diagnosed with cancer. Decisions in this context are particularly complex and multifaceted. In this Review, we aim to provide an overview of the key points to address when making a treatment strategy in these patients. We provide information on what happens if dialysis is not started or is stopped, and how physicians should deal with such patients. Informed decisions about dialysis require a personalised care plan that considers the prognosis and treatment options for each condition while also respecting patient preferences. The concept of prognosis should include quality-of-life considerations, functional status, and burden of care. Close collaboration between oncologists, nephrologists, and geriatricians is crucial to making optimal treatment decisions, and several tools are available for estimating cancer prognosis, prognosis of renal disease, and general age-related prognosis. Emerging evidence shows that these geriatric assessment tools, which measure degrees of frailty, are useful in patients with chronic kidney disease. In this Review, we try to hand tools to practising physicians, to guide decision making regarding the initiation and termination of dialysis in patients with advanced cancer.

Introduction

In an ageing population, cancer and kidney disease are both growing public health concerns and are closely connected.[1] Because of reduced cardiovascular mortality people tend to live longer, and the incidence and prevalence of both kidney disease and cancer increases with age. Currently, about half of the patients newly diagnosed with cancer are older than 65 years and epidemiological research predicts a substantial increase in older patients confronted with cancer in the coming decades.[2] At the same time, the incidence of end-stage kidney disease (ESKD) in the ageing population has increased steadily in the past decades, resulting in a growing number of older patients starting dialysis.[3,4] According to the European Renal Association-European Dialysis and Transplant Association annual report of 2016, 27% of patients initiating renal replacement therapy were older than 75 years, and constituted one of the fastest growing age groups initiating dialysis.[3] Two clinically relevant situations can occur. First, patients with a known cancer can develop ESKD and the question of whether to start dialysis can come up at some timepoint. Second, for patients with ESKD on dialysis who develop cancer, the decision to continue with dialysis might be questioned at some timepoint. Older patients with ESKD are likely to have multiple comorbidities, and a substantial proportion of these patients show functional and cognitive impairment[5,6] or lose their personal independence within the first months or years on dialysis.[7] However, there is substantial heterogeneity in the ageing process, resulting in important variations in treatment patterns and outcomes in older patients. There is little evidence about what to base treatment decisions on for older patients with cancer and kidney dysfunction, because this group is notably under-represented in clinical trials.[8,9]

Because chronological age alone is a poor descriptor of heterogeneity in the ageing process, a systematic and evidence-based way of evaluating an individual's health and resilience is needed to guide oncology treatment decisions. Comprehensive geriatric assessment (CGA) has been proposed as an approach to fill this knowledge gap.[10] CGA is defined as a multidimensional, interdisciplinary diagnostic process focused on determining an older person's medical, psychosocial, and functional capabilities. The interdisciplinary team that does CGA is led by a geriatrician and can also include a specialised nurse, physiotherapist, dietitian, occupational therapist, and a social worker. With this objectively gathered CGA information, the medical team is able to develop a coordinated and integrated plan for treatment and long-term follow-up.[11] CGA provides a solid base for shared decision making, because it gathers information about the functional and psychosocial capabilities and limitations that are linked to discussing what matters most in the individual patient's daily life. In the general (ie, non-oncological) older population, CGA-guided treatment plans have been shown in some, but not all, studies to improve overall survival, quality of life, and physical function, and to decrease the risk of hospitalisation and nursing home placement.[12–14] In the oncology field in the past, CGA research mainly studied the diagnostic process and assessment (also known as the geriatric assessment),[15] without integrating the holistic geriatric intervention and follow-up approach that is crucial in the whole CGA process. In the past decade, several trials in older patients with cancer showed that geriatric intervention had a clear benefit.[16] Given the complicated setting of both cancer and kidney disease (and possible frailty), in this population it is strongly recommended not to use geriatric assessment only. Instead, it is better to take advantage of the full CGA

process to provide the best care, and ideally to include renal-specific members (eg, dialysis nurse educators and dialysis social workers) in the CGA interdisciplinary team. Eastern Cooperative Oncology Group (ECOG) Performance Status and Karnofsky Performance Status scores are quick and simple to ascertain but do not have enough sensitivity to detect frailty efficiently. Furthermore, these measurements do not have detailed information on the exact severity of geriatric problems in different domains. In a study by Hurria and colleagues,[17] the Karnofsky Performance Status was not able to predict chemotherapy toxicity, whereas geriatric assessment components added substantial value in predicting chemo toxicity.

The connection between cancer and kidney disease

The incidence of acute kidney injury and chronic kidney disease in patients with cancer is higher than in the non-cancer population as a consequence of the cancer itself (eg, as a result of multiple myeloma, urinary obstruction, cancer-induced nephropathy), its treatment (eg, tumour lysis syndrome, drug-induced nephropathy, surgery), or severe complications (eg, sepsis, dehydration, contrast nephropathy, diffuse intravascular coagulation).[18] In a cross-sectional analysis of 3558 patients with cancer admitted to MD Anderson Cancer Centre, a comprehensive cancer centre in Houston, Texas, USA, 12% had acute kidney injury (using the modified RIFLE criteria[19]) compared with 5–8% in populations without cancer.[20] Development of acute kidney injury in patients with cancer was associated with 2 times longer hospital stays, 2·1 times higher costs, and 4·5 times the risk of death.[20] In the intensive care unit, the incidence of acute kidney injury is also higher in people with cancer, and is associated with lower survival rates, than in people without cancer.[21] Sometimes acute kidney injury requiring renal replacement therapy is the presenting symptom of cancer (eg, cast nephropathy in multiple myeloma). In this setting, renal replacement therapy should be recommended to allow time in which to evaluate the effect of anti-cancer treatment, because acute kidney injury might be reversible in such cases with the initiation of effective chemotherapy.

Similar to acute kidney injury, chronic kidney disease is also more common in patients with cancer than in patients without, according to the Renal Insufficiency and Anticancer Medications study by Launay-Vacher and colleagues,[22] which reported that 50–60% of patients with cancer also had chronic kidney disease. The presence of chronic kidney disease affects not only potential treatment options, but also the effectiveness of treatment and overall survival in specific cancers.[22] It should be acknowledged that decreased renal function also influences the appropriate dose for several renally excreted agents such as chemotherapy,[23,24] and that relevant data from clinical trials in cancer are scarce, because patients with estimated glomerular filtration rate (eGFR) less than 30mL/min are systematically excluded from such trials.[9] Moreover, renal replacement therapy has an important effect on many anti-cancer drugs; however, a detailed discussion of this topic is beyond the scope of this Review.

The association between cancer and kidney disease is further evidenced by the reported higher incidence of cancer in patients with chronic kidney disease and ESKD compared with the corresponding general population. Not all cancer types are equally over-represented, and studies show the strongest association is with the development of renal cell carcinoma.[25–27] In a retrospective cohort study by Lowrance and colleagues,[28] a lower eGFR was associated with an increased risk of renal cell carcinoma (adjusted hazard ratio 2·28, 95% CI 1·78–2·92 for an eGFR <30 mL/min per 1·73 m²). In patients with ESKD on dialysis, the observed increased risk for renal cell carcinoma is related to the development of acquired cystic disease of the kidney, which increases with time on dialysis.[27] Although age-related screening for colon cancer, cervical cancer, and breast cancer has been advocated for patients on dialysis,[29] the absolute benefit in such a population is highly questionable.[30] Even the routine screening of patients on dialysis for renal cell carcinoma remains controversial at best, given its low incidence and the low expected survival of patients on dialysis. Screening should be individualised after considering the general health condition and life expectancy of the patient.[30]

Not starting dialysis, or stopping dialysis, is a valid treatment option in older people with cancer

The general public considers dialysis to be life-saving, but regretfully this treatment can only be viewed as life-prolonging, and it worsens quality of life while increasing the burden of care. Many patients with ESKD are frail and have multiple comorbidities. Overall survival of patients on maintenance dialysis remains low, with a 5-year survival rate of 46·9%; however, there is high interindividual variation depending on age, functional status, and presence of specific comorbidities at the time of initiating renal replacement therapy.[31,32] Besides the medical complications, it is well established that the initiation of renal replacement therapy is associated with a sudden functional decline and decrease in quality of life.[7,33] Functional status is an outcome that matters to older patients, the majority of whom prioritise functional status over life prolongation.[34] Furthermore, patients on dialysis are more likely to die in a hospital than in hospice care, and most patients on dialysis receive aggressive treatment in the last years of life.[35] It is important to acknowledge that dialysis regret is common. For example, Saeed and colleagues[36] found that decisional regret occurred in 82 (21%) of 397 patients receiving maintenance dialysis. Conservative management has become an accepted alternative to dialysis.[35] This development was illustrated by Verberne and colleagues,[37,38] who

retrospectively compared outcomes for conservative care versus renal replacement therapy in 311 Dutch patients aged 70 years or older. While this study found that patients aged 70 years or older who had renal replacement therapy had significantly longer survival than those who chose conservative care median, 75th to 25th percentiles: (median time since date of care decision 3·1 years [IQR 1·5–6·9] *vs* 1·5 years [0·7–3·0] respectively; log-rank p<0·001), no significant difference was observed in the subgroup of patients aged 80 years or older (2·1 years, IQR [1·5–3·4] *vs* 1·4 years [0·7–3·0] log-rank p=0·08, respectively). Moreover, while patients who were aged 70 years and older with severe comorbidity (ie, Davies comorbidity score ≥3) who chose renal replacement therapy still lived significantly longer than those who chose conservative care, the survival difference was smaller than for those with fewer comorbidities (1·8 median years survival from treatment decision choice [IQR: 0·7–4·1] *vs* 1·0 [0·6–1·4]; log-rank p=0·02)[37] Not starting dialysis, or stopping dialysis, is therefore a valid treatment option in older people with cancer, particularly if the cancer prognosis or general age-related prognosis is unfavourable. The medical team has an ethical obligation towards the patient to delineate the diagnosis and to highlight the option for dialysis without omitting information on the risk–benefit ratio. Likewise, the alternative possibility of a conservative approach with obligatory palliative care should be described. Patients have the right to forego any treatment, although they cannot force the medical team to offer a therapy argued to be futile. Renal replacement therapy only prolongs life and buys time to await tumour regression or kidney function recuperation, if either is anticipated. A time-limited dialysis trial can be advocated, after which the patient can decide whether or not to continue. The patient then takes the ultimate decision to stop dialysis when they feel that everything has been said and done and that the time to die has arrived.

In clinical practice, different scenarios can be envisaged. First, patients with a known cancer might develop ESKD. Alternatively, patients with ESKD on dialysis might develop cancer, for whom the decision to pursue dialysis could be questioned at some timepoint. In the first scenario, it will be important for the patient and oncologist to understand the effect of ESKD, and to get an idea about the prognosis with and without dialysis, so they can make an informed decision about initiation of dialysis. In the second setting, other questions become relevant—ie, what are the diagnostic and therapeutic options, and what is the (suspected) cancer-prognosis? In patients with frailty, who have few therapeutic options irrespective of the type of cancer, it is particularly important to consider the benefits and harms of diagnostic procedures as part of the ultimate decision-making process.

Of course, some questions will be relevant irrespective of the setting (see panel 1).

***Panel 1*: Questions to ask about older patients with cancer who are considering not starting dialysis, or stopping dialysis**

What is the prognosis of the patient, given their current frailty, overall health status, and comorbidities? How is this affected by the cancer, with and without treatment?

What will be the effects of the possible oncological treatment options for this specific patient, given their frailty status? What does this mean for the oncological treatment decision?

What is the prognosis for the end-stage kidney disease, with and without dialysis?

What is the expected effect of starting or withholding dialysis in this particular patient, given their frailty status? What does this mean for the treatment decision?

How much of the patient's current frailty status is determined by symptoms of their cancer or end-stage kidney disease, which could be alleviated by starting treatment?

What happens if the patient does not start dialysis or anticancer therapy?

To guide the discussion with the patient, information about the future evolution of the disease is needed, and specifically, information from three different viewpoints—the oncology, geriatric, and renal perspectives. From the oncology viewpoint, oncologists need to inform the patient about the expected disease development, with and without starting or continuing anticancer therapy. From the geriatric viewpoint, geriatricians are best placed to inform patients about the possible effects on independence, functionality, and quality of life in general for a person of their age and degree of frailty (further coverage is beyond the scope of this Review). From the renal perspective, renal prognosis is an important preamble in discussions with the patient, and is determined by residual renal function and the severity of the underlying renal pathology. Although hardly exact, the nephrologist can estimate a disease evolution and can mention a projected renal life of days, weeks, or months. Validated prognostic tools can assist in this context, for example, the Kidney Failure Risk Equation.[39,40] The uraemic picture evolves gradually, originating from the declining renal excretory and homoeostatic capacity. Starting renal replacement therapy only partially alleviates this broad spectrum of symptoms. Moreover, the non-renal co-morbidity of these older patients aggravates and contributes to their problems. In light of the declining cognition that accompanies deteriorating renal function, it is important to begin discussions about the initiation or termination of dialysis as early as possible in the patient's clinical course, to allow for informed decision making.

For more on **The Kidney Failure Risk Equation** see https://kidneyfailurerisk.com

Panel 2 gives an overview of anticipated uraemic symptoms and treatment approaches.[41,42] Most often, the earliest symptom is tiredness, indiscernible from fatigue caused by the comorbid neoplastic disease, deconditioning, or as a feature of patient frailty. This daylong tiredness is multifactorial and linked to anaemia, or to anorexia with muscle atrophy and heart failure or heart failure alone. Illness-related exhaustion and sleep disorders are also quite common. Other important symptoms are a diminished

***Panel 2*: Supportive therapies for treating the symptoms of patients with cancer, emphasising conservatively managed chronic kidney disease[41–48]**

Psychosocial symptoms

Fatigue or drowsiness

- Management of sleep disorders (see sleep disorders below)
- Treat nutritional deficiencies (eg, protein or caloric malnutrition, iron, vitamins)
- Set realistic blood pressure targets; if arterial stiffness or orthostatic hypotension are anticipated, apply upper limit of 160/90 mm Hg
- Stimulating daily low-intensity aerobic exercises
- Avoid sedative side-effects of renally cleared drugs (eg, sustained-release tramadol; high-dose gabapentin or pregabalin)
- Some authors advocate supraphysiological doses of levocarnitine but there are few convincing trials

Sleep disorders

- Educational efforts to improve sleep hygiene
- Treatment of sleep disturbing symptoms (nocturia, pruritus, muscle cramps, restless legs)
- Low-dose gabapentin or pregabalin at night
- Sedative antidepressants (eg, trazodone, mirtazapine, doxepin)
- Simple sedatives (eg, zolpidem, zopiclone)

Weakness associated with sarcopenia, anaemia, and anorexia

- Alleviate associated conditions

Difficulty concentrating, associated with sleep disorders and depression

- Treat associated conditions

Depression, worrying, or feeling sad or irritable

- Non-pharmacological interventions: cognitive behavioural therapy, exercise, improvement of sleep
- Classic pharmacological interventions, (eg, fluoxetine, sertraline, citalopram, escitalopram) have not been shown to be effective in managing these symptoms in this patient population

Anaemia

- Restrictive transfusion policy
- Restrictive use of erythropoiesis-stimulating agents

Sexual dysfunction

- Targeted therapy

Gastrointestinal anorexia, decreased appetite

- Treat stomatitis
- Institute proper oral hygiene
- Stop dietary restrictions
- Adjust food taste to suit the individuals' preferences
- High-calorie liquid supplements with reduced potassium and phosphorus content

Nausea, vomiting

- No evidence-based therapy in chronic kidney disease but symptomatic interventions can be tried:
  - First line: odansetron
  - Second line: metoclopramide
  - Third line: olanzapine or haloperidol
  - Fourth line: high-dose haloperidol or high-dose methotrimeprazine

Diarrhoea

- Exclude or treat organic pathology or gastrointestinal infections
- Symptomatic interventions can be tried (eg, probiotics, loperamide)

Constipation

- Symptomatic interventions can be tried (eg, increased dietary fibre, osmotic laxatives)

Dry mouth, halitosis

- Avoid drugs with anticholinergic side-effects or centrally mediated reduction of saliva secretion (eg, clonidine, oxybutynin)
- Treat stomatitis and gingivitis
- Institute proper oral hygiene
- Advise mouth wash
- Acupressure to stimulate salivary glands
- Prescribe oral spray with saliva substitutes
- Some drugs can stimulate saliva flow (eg, pilocarpine, cevimeline, drugs targeting angiotensin II)
- If restricted fluid intake is warranted, advise sugarless chewing gum, peppermints, or small quantities of ice-cold or frozen beverages

Pain symptoms

Uraemic pruritus or itching

- Exclude allergic reactions and cutaneous infections
- Optimise haemoglobin and iron status
- Topical treatment (emollients, hydrating ointments containing menthol–camphor–phenol 0·3%, gamolenic acid 2·2%, capsaicin 0·025% or 0·03%, or pramocaine 1%)
- Ultraviolet B phototherapy
- Systemic treatment (low-dose gabapentin or pregabalin; tricyclic antidepressant, or sedating antihistamine—eg, desloratadine)
- A phase 3 trial[49] of difelikefalin showed a significant reduction in itch intensity and improved itch-related quality of life in patients with pruritus on haemodialysis

Dry skin

- Hydrating ointments (see topical treatments above)

Haematoma

- Avoid accumulation of low-molecular-weight heparins
- Critical appraisal of indication and dose of oral anticoagulants and antiplatelet drugs

Restless legs

- Avoid dopamine antagonists, some antidepressants, and opioids

(Panel 2 continues on next page)

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- Avoid alcohol, caffeine, and nicotine
- Correct hyperphosphataemia and iron deficiency
- Non-pharmacological interventions: treatment of sleep disorders, low-intensity exercise, and pneumatic compression devices
- Pharmacological interventions:
  - First line: low-dose gabapentin or low-dose pregabalin
  - Second line: ropinirole, pramipexole, or rotigotine

Numbness or tingling in feet or neuropathic pain caused by drug-related side-effects (not by uraemia)

- Start with adjuvant therapy:
  - First line: low-dose gabapentin or low-dose pregabalin. Low-dose duloxetine can be used in moderate to severe renal impairment but is not recommended in end-stage kidney disease
  - Second line: amitriptyline or doxepine
- Proceed with additional analgesics:
  - First line: weak opioid—eg, low-dose tramadol
  - Second line: strong opioid, preferably hydromorphone; alternatives are fentanyl, buprenorphine, or methadone

Muscle cramps or muscle soreness

- Stop statins
- Minimise diuretic dose
- Correct electrolyte and acid-base abnormalities (metabolic acidosis, hypocalcaemia, hypophosphataemia, and hypomagnesaemia)
- Low-dose benzodiazepines
- Some studies report a beneficial effect of supraphysiological doses of levocarnitine and a short course of vitamin E supplementation
- Beware of over-the-counter drugs containing quinine because of possible side-effects (ie, prolonged QTc, haemolytic uraemic syndrome)

Headache, bone or joint pain, existential pain

- WHO analgesic ladder taking pharmacokinetic data into account:
  - First line: paracetamol
  - Second line: topical nonsteroidal anti-inflammatory drugs; avoid systemic nonsteroidal anti-inflammatory drugs
  - Third line: add opioids. Hydromorphone has a favourable risk–benefit ratio in end-stage kidney disease; alternatives are fentanyl, buprenorphine, or methadone.

Poor mobility

- Treat joint pain as needed
- Alleviate muscle soreness
- Suggest commencing low-intensity aerobic exercise

Cardiopulmonary symptoms

Oedema, swollen legs

- Avoid liberal salt and fluid intakes
- High-dose loop diuretics titrated on the basis of effectiveness and side-effects

Dyspnoea, shortness of breath, cough, chest pain

- Treat anxiety
- Treat metabolic acidosis with oral sodium bicarbonate
- Optimise haemoglobin and iron status
- High-dose loop diuretics
- Nitrates
- Oxygen therapy
- Discuss appropriateness of therapy escalation—eg, non-invasive or invasive ventilation
- In case of imminent death, proceed to palliative sedation comprising midazolam and either opioids or fentanyl

attention span, feelings of depression, true clinical depression, and feelings of being a burden to relatives. Patients with chronic kidney disease usually lose appetite and can also have nausea or vomiting. Of course, some chemotherapeutic regimens can contribute to, or aggravate, these symptoms by causing mucositis or moniliasis. Diarrhoea and constipation are frequent symptoms in chronic kidney disease. Dermatological symptoms are common and include skin dryness and itching, subcutaneous bleeding, and even frank haematomas after minor trauma. Electrolyte abnormalities can elicit muscle cramps. Uraemic polyneuropathy and iron deficiency can cause restless legs and burning feet sensations. Regretfully, pain is a frequent symptom and detailed information on type and dose of analgesic drugs is useful in patients with cancer and renal insufficiency. The pain these patients have can result from the neoplastic process itself, the weight loss, and growing immobility with stiffness of the joints and evolving bedsores. Although the limited survival of these patients does not often allow for the development of uraemic neuropathy, neuropathy related to chemotherapy can appear, especially with specific drugs, such as taxanes, vinca alkaloids, platinum derivatives, bortezomib, and thalidomide. Finally, a positive fluid balance can occur, resulting in oedema and dyspnoea.

How should physicians deal with patients when dialysis is not started or is stopped?

Providing information is essential, and patients deciding whether to start or whether to stop dialysis should be informed of their prognosis and possible symptom burden. At this time, maximal conservative management is offered as an alternative. This approach encompasses supportive treatment to alleviate the symptom burden in patients with ESKD, plus measures to preserve residual renal function.[50] These measures include avoiding prolonged hypotension, nephrotoxic agents (eg, non-steroidal anti-inflammatory drugs), and procedures

involving intravenous contrast agents. Symptom assessment tools are important to guide and evaluate treatment, and a multitude of symptom assessment tools is currently available. A study by Van der Willik and colleagues[51] looked at 121 symptom assessment questionnaires, and identified the Dialysis Symptom Index[52] as the best in its class. The Integrated Palliative Care Outcome Scale-Renal[53] is an alternative symptom scale, but can take longer to complete. Symptom treatment, as described in panel 2, encompasses adaptation of common drugs to the reduced kidney function, although there is little reliable pharmacological data to guide these decisions.[23] Drug formulations with delayed absorption should be avoided, and low starting doses are recommended.

The delicate balance between treating and alleviating in these circumstances has kindled the rapidly evolving subspecialty of onconephrology, which through dialogue centralises expertise from both fields.[54] Discussing end-of-life issues with patients requires specific skills, which should be taught during the nephrology fellowship.[55,56] To make these important treatment decisions, it is crucial to have timely discussions between patients, family members or caregivers, and practitioners, about the delicate topics of prognosis and patient preferences. Advance care planning delineates the boundaries of therapeutic perseverance according to the patients' preferences[57] and aims to prepare patients and their caregivers for end-of-life decision making, in an attempt to enhance quality of life, without necessarily extending it.[58] After advanced care planning conversations, patients can limit therapeutic escalation. As a first step, the medical team confirms it will not resuscitate the patient and to forego giving futile treatment. Sudden death is not uncommon in these patients and can sometimes be embraced by family and caregivers. Enteral feeding and invasive ventilation prolong suffering and are considered futile. In the context of oncological comorbidity, kidney disease, and advanced age, it is anticipated that the wellbeing of most patients will decline quickly. Uninformed patients might fear renal death, especially if they hold the false presumption that they will die due to asphyxiation as a result of pulmonary oedema. More often, patients will become bedridden, anxious, delirious, and agitated. Axelsson and colleagues reported that in 472 patients approaching renal death, a high prevalence had pain (69%), followed by bronchial secretions (46%), anxiety (41%), confusion (30%), shortness of breath (22%), and nausea (17%).[59,60] It should be stressed that all of these symptoms can be palliated with medication. In line with our own experience, Catalano and colleagues[61] reported that the median survival after dialysis withdrawal was 8 days. Patients retaining their capacity to make decisions sometimes prefer euthanasia, which is a lawful option in some countries, including Belgium, the Netherlands, Luxemburg, Canada, and Colombia. Physician-assisted suicide is also legal in ten US states. However, when the vital prognosis is short and symptom control is acceptable, medically-assisted death diverges from uraemic death only by a few days. During these last days, the load of uraemic symptoms often imposes a high need of sedative and analgesic treatment that complies with the guideline standards for palliative sedation. These options should be discussed with the patient and family.

For more on **ePrognosis** see https://eprognosis.ucsf.edu/

Prognostication of older patients with ESKD and cancer

Considering the high burden of dialysis treatment and the absence of clear survival advantage in older patients, conservative care should be regarded as an accepted alternative to dialysis, especially in frail older patients with cancer. But how can physicians and nephrologists discriminate between fit and frail older patients to select those who are more likely to benefit from conservative care? There is no consensus about a single, standardised, easily adapted approach for older patients with ESKD or about which prognostic tools to use. However, predictive information about survival after initiating dialysis is important for patients in the decision-making process. These discussions and the decision process require time and for trust to exist between the patient, family, and treatment team. In patients with chronic kidney disease, usually there is a longstanding therapeutic relationship between the nephrologist and the patient, and therefore nephrologists should be actively involved in joint discussions that take patient priorities into account and allow for some time for consideration. The complexity of this setting is that the global prognosis (ie, the anticipated course of living with an illness[62]) is determined by at least three factors, which are partly independent: the cancer prognosis, the frailty-associated prognosis (which includes other comorbidities, functional status, and geriatric syndromes), and the prognosis based on the renal disease (see figure). However, prognosis is more than life expectancy alone; a broader definition is to consider prognosis as the anticipated course of living with an illness.[62] In serious illness, several dimensions other than life expectancy have to be considered and acknowledged when making decisions, such as quality of life, burden of care, functional status, the patients' own hopes and worries, and the possibility of unpredictable events.

CGA is currently the gold standard for evaluating the global health status and clinical frailty of individuals, and several tools have been developed separately to estimate prognosis, which are discussed next.

For the general geriatric population, prognostic tools are available (eg, ePrognosis) that can be selected on the basis of patient setting (eg, nursing home, hospital, ambulatory setting) and preferred time horizon (eg, 3-month, 4-year, or 10-year survival). Most evidence about the effectiveness of these tools comes from acute hospital settings.[12,67] Inpatient assessments and related interventions have shown reductions in length of stay, mortality, readmission rates, and costs.[68] Emergency department assessments can reduce acute admissions

and increase referrals to palliative and hospice care.[68] Using these tools as part of preoperative protocols is associated with better patient outcomes, particularly after hip fracture.[69] Some of these tools include global assessment of cancer or renal disease (ie, present or absent); they provide very imprecise information about either condition, but can be useful for obtaining a global estimate of life expectancy.

In the oncology field, there are many data on prognostic factors of survival in different tumour types (discussion of this is beyond the scope of this Review). Age is often among these prognostic factors, but tumour related factors (eg, tumour characteristics, extent of disease) are generally more important, and frailty is rarely included because it was not often measured in previous studies. Subsequent oncological studies started to integrate frailty parameters (measured by geriatric assessment) when looking at prognosis and treatment tolerance. Geriatric assessment in older patients with cancer is able to detect unidentified problems and risks to which targeted interventions can be applied, predict adverse outcomes (eg, toxicity, functional or cognitive decline, postoperative complications), and estimate residual life expectancy and the lethality of the malignancy in the context of competing comorbidities and general health problems.[70] For example, two large prospective studies—Cancer and Aging Research Group (CARG)[65] and Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH)[66]—identified parameters of geriatric assessment capable of predicting severe chemotherapy-related complications in a heterogeneous cancer population. Therefore, several organisations like the International Society of Geriatric Oncology, the European Organisation for Research and Treatment of Cancer, and the American Society of Clinical Oncology recommend that some form of CGA should be mandatory to guide oncological treatment decisions.[70–72] Several studies showed that most components of the CGA have independent prognostic value for survival (eg, functional status,[15,73] nutritional status,[8,40,74,75] and mental health[15,73]), with nutrition consistently among the strongest predictors of outcome. However, a complete CGA is time consuming, therefore to select the patients who would benefit the most from geriatric assessment, a number of geriatric screening tools have been developed (eg, Geriatric 8 [also known as G8],[76] the Vulnerable Elders Survey 13,[77] and the Flemish version of the Triage Risk Screening Tool[78]). Some of these tools can also provide important information about treatment–related toxicity, the risk of functional decline, and overall survival.[78–82] Screening tools do not replace geriatric assessment but are recommended for use in busy practices, to identify those patients in need of full geriatric assessment. Nevertheless, as stated earlier, in the setting of both cancer and kidney disease (and possible frailty), it is strongly recommended that the full CGA process is used.

In the dialysis population, several tools have also been evaluated to estimate prognosis (table). Also, in patients with advanced kidney disease, there are reports that geriatric assessment is useful to inform shared decision making regarding modality choice and to maximise opportunities for rehabilitation and maintenance of independence.[84,85] It has been suggested that CGA should be done, and advanced care planning applied, at the time of dialysis initiation and then adjusted when a major change in a patient's health or functional status occurs, such as a hospitalisation.[84]

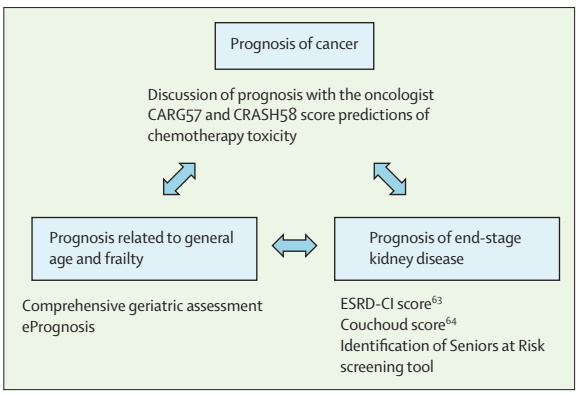

Figure: **Factors to consider when dealing with older people who have cancer and end-stage kidney disease**
The prognosis is determined by the cancer-related prognosis, the age-related prognosis, and the end-stage kidney disease prognosis. The results of these different prognostications need to be combined to arrive at an integrated prognosis. CARG=Cancer and Aging Research Group.[65] CRASH=Chemotherapy Risk Assessment Scale for High-Age Patients.[66] ESRD-CI=End-Stage Renal Disease Comorbidity Index score.[63]

In 2003, Hemmelgarn and colleagues[63] published the End-Stage Renal Disease Comorbidity Index (ESRD-CI), a modified Charlson Comorbidity Index (CCI)[83] specifically designed for patients with ESKD on dialysis, which was slightly better at predicting survival in the dialysis population than the original CCI. 18 comorbidities were included in the ESRD-CI (renal disease was excluded because it was present in the whole study population). The improvement in predictive ability with the ESRD-CI compared with the CCI was related to assigning different weightings to the comorbidity variables specific for the dialysis population. Lymphoma and metastatic disease were the strongest predictors of death in both univariate and multivariate analyses, and received even higher weighting than in the original CCI, whereas the presence of a non-metastatic solid organ tumour was discarded in the newer ESRD-CI.[63] This change underlines the importance of the cancer type and stage on overall prognosis.

Another prognostic tool was developed in 2015 by Couchoud and colleagues,[64] in an attempt to identify older patients at high risk of mortality within the first 3 months after initiating dialysis. Patients were grouped by risk classification score (low ≤12; intermediate 12–16; high 17–25) and mortality was less than 20% in the low group, 20–40% in the intermediate group, and over 40% in the high group.[64] Remarkably, in this prognostic tool cancer was only registered as either present or absent, without further staging or specification, and

	Weighted score
End-Stage Renal Disease Comorbidity Index[63]	
Myocardial infarction	2
Congestive heart failure	2
Peripheral vascular disease	1
Cerebral vascular disease	2
Dementia	1
Chronic lung disease	1
Rheumatological disease	1
Peptic ulcer disease	1
Diabetes without complications	2
Diabetes with complications	1
Moderate–severe liver disease	2
Metastatic disease	10
Leukaemia	2
Lymphoma	5
Couchoud score[64]	
Male gender	1
Age, years	
85–90	2
≥90	3
Congestive heart failure	
NYHA I–II	2
NYHA III–IV	4
Peripheral vascular disease 3–4	1
Dysrhythmia	1
Cancer	2
Severe behavioural disorder	2
Mobility	
Needs assistance to transfer*	4
Totally dependent for transfer*	9
Albuminaemia, g/L	
<25	5
25–30	3
30–35	2

The End-Stage Renal Disease Comorbidity Index devised by Hemmelgarn and colleagues[63] is a modified Charlson Comorbidity Index.[83] NYHA=New York Heart Association Classification. *Transfer means a patient moving from one place to another (eg, getting out of bed and into a wheelchair).

Table: **Score weighting for comorbidity variables used in two prognostic tools for end-stage renal disease**

was designated a relatively low risk score.[64] This low risk was probably because the tool only predicts up to 3-month survival, compared with the 10-year survival prediction capability of the ESRD-CI. The important advantage of the prognostic tool developed by Couchoud and colleagues is the inclusion of other comorbidities, age, mobility, and serum albumin level, which can be considered surrogates for frailty.

Different geriatric assessment screening tools were evaluated in a study by Van Loon and colleagues.[86] The Identification of Seniors at Risk screening tool had the best discriminating abilities to predict the outcome of the geriatric assessment, with a sensitivity of 74%, a specificity of 80%, a positive predictive value of 91%, and a negative predictive value of 52%.[86] The study found that the negative predictive value was poor for all tools, which means that almost half of the patients who were screened as fit (ie, non-frail) were found to have two or more geriatric impairments in the geriatric assessment. The same group has published on the prognostic value of geriatric assessment in patients starting dialysis, both for survival, quality of life, and health-care consumption.[87–89] European Renal Best Practice[90] recommends "a simple score be used on a regular basis to assess functional status in older patients with [chronic kidney disease] stage 3b–5d with the intention to identify those who would benefit from a more in-depth geriatric assessment and rehabilitation program". The International Society of Peritoneal Dialysis expert opinion is that geriatric assessment is crucial in establishing what possible barriers are present that might affect successful peritoneal dialysis, and in establishing a care plan to promote maximum functionality.[91]

Conclusion and perspectives

Both cancer and kidney disease predominantly affect the older population. Therefore, physicians are increasingly faced with treatment decisions in older patients with cancer with advanced kidney disease. In this setting, the cancer prognosis competes with renal and other (age-related) causes of death, therefore prognostication of cancer, kidney disease, and other conditions should ideally be taken into account simultaneously. Furthermore, the concept of prognosis needs to include quality-of-life considerations, functional status, and burden of care. On the basis of all these considerations, the physician might aid the patient in making decisions that make sense to the patient in their own life. It is crucially important for clinicians and patients to be informed about the prognosis of these co-existing illnesses by consulting other treating clinicians, thereby providing a better perspective of what dialysis initiation will do to the overall health state of the patient.[13] The complexity of this setting is that the global prognosis is determined by at least three largely independent factors, namely the cancer prognosis, the frailty-associated prognosis (which includes other comorbidities and geriatric syndromes), and the prognosis based on the kidney disease. For some patients the prognosis might be mostly determined by frailty, for others by the cancer, and by the kidney problem for some others. CGA is a multidisciplinary and multidimensional diagnostic process in which medical, nutritional, functional, and psychosocial capabilities are evaluated. Geriatric assessment can help to detect unrecognised geriatric problems, enable earlier intervention, and lead to increasingly individualised treatment strategies. There is general consensus that a geriatric assessment is the best systematic approach for the identification of frailty in clinical practice,[80] and we highly recommend the use of CGA to guide treatment decisions in the complex setting

Search strategy and selection criteria

We searched PubMed on March 3, 2020, using the search terms "dialysis initiation", "dialysis termination", "cancer", "elderly", "frailty", "comprehensive geriatric assessment", "prognostic tool", AND "advanced care management" for articles published in English from inception to July 15, 2020. We also included articles identified through searches of our own files. We generated the final reference list on the basis of originality and relevance to the broad scope of this Review.

of patients with cancer, chronic kidney disease, and frailty. Different prognostic tools have been developed for the general geriatric population, the oncological population, and the dialysis population, which can help to guide this decision-making process. There is no universal set of tools, but rather a consensus on which domains need to be assessed. Various geriatric assessment tools are available and it is strongly recommended that practising physicians should use the tools that are most appropriate in their context and with which they are familiar. Shorter, less time-consuming tools such as the G8 screening tool or other short evaluations can be used, but it should be acknowledged that they do not provide detailed insight into the specific geriatric problems, which might be problematic in the complex setting of cancer, frailty, and renal insufficiency. Prognostication in the setting of an older patient with cancer on dialysis is not easy, and no single prognostic tool can accurately predict outcome. Therefore, multidisciplinary discussion between the different involved specialists about individual patients is important. For many patients, it is possible to clarify which domain is likely to be the most life threatening. It might be relevant to estimate prognosis for each different condition separately and to discuss all this information in a multidisciplinary context. The decision to provide conservative care only has to be made in each different domain separately—eg, does anticancer therapy need to be continued or not, should dialysis be started or not? These decisions might all be linked, for example, a decision not to start dialysis also has consequences for the decision to proceed with anticancer therapy or to start a revalidation. It is clear that the prognostic capacity for survival of existing geriatric assessment-based models such as ePrognosis[92] should be explored in older populations with cancer and advanced kidney dysfunction.

Contributors

BS, AVdV, BdM, and HW contributed to the conception and design of the Review. BS, AVdV, BdM, and HW did the literature search and constructed the panels and figure. MEH, SR, SL, and SML contributed to the literature review. BS, BdM, and HW drafted the paper and interpreted the included search results. All authors contributed to data interpretation and the rewriting of the Review and reviewed and approved the final version.

Declaration of interests

HW declares consulting fees and honoraria from AbbVie, Amgen, Ariez International, AstraZeneca, Biocartis, Celldex Therapeutics, DNA Prime, Janssen-Cilag, Lilly, Novartis, Orion Corporation, Pfizer, The Planning Shop, Puma Biotechnology, Roche, Sirtex, TRM Oncology, and Vifor Pharma; travel support from Roche, Pfizer, Nippon Travel Agency, Congress Care, DNA Prime, and Global Teamwork, and a research grant from Novartis paid to his institution. All other authors declare no competing interests.

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