ORIGINAL ARTICLE

Port J Nephrol Hypert 2016; 30(4): 291-297 • Advance Access publication 28 December 2016

Cancer and End-Stage Kidney Disease: A Death Sentence?

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Received for publication: Oct 11, 2016
Accepted in revised form: Dec 7, 2016

ABSTRACT

Background: End-stage kidney disease is associated with considerable morbidity and mortality, a feature that is shared with malignant neoplasms. Hence, patients with the cumulative effect of these two diseases frequently give rise to the question of whether dialysis should be implemented. The primary goal of this study was to characterize the clinical progression and evaluate the outcome of a group of oncology patients on chronic haemodialysis and also to identify the characteristics associated with prolonged survival. **Methods:** Retrospective analysis of all patients on the chronic haemodialysis programme in an oncology hospital-based haemodialysis centre between January 1991 and September 2014. **Results:** 141 patients were treated during this period. The main aetiologies for end-stage kidney disease were multiple myeloma (24.8%) and chronic interstitial disease (22.7%), while the most common tumours were genitourinary cancer (47.5%) and multiple myeloma (24.8%). Multiple tumours were present in 22.0% of patients and 19.2% harboured metastatic disease. Overall, 66.7% of patients died during this period; 7.8% were transferred to other centres as a result of clinical stability; 4.3% recovered renal function; 1.4% received a kidney transplant and 19.9% were still alive at the end of the study. Overall survival was 58.8% at 2 years and 34.8% at 5 years. Multiple myeloma (HR=5.950; 95% CI: 2.512-14.092) and gastrointestinal cancers (HR=3.277; 95% CI: 1.176-9.134) were associated with increased likelihood of death. **Conclusions:** Survival among patients with often locally advanced or metastatic oncological disease on chronic haemodialysis was unexpectedly high, with 1/3 still alive at 5 years. Accordingly, decision-making in the cancer setting must be individualized, integrating clinical assessment, accurate prognostication and treatment options in each particular case.

Key words: cancer, end-stage kidney disease, haemodialysis, prognosis, survival

INTRODUCTION

End-stage kidney disease (ESKD) is associated with a known burden of morbidity and mortality[1], a finding also observed with malignant diseases[2]. Due to improvements in the management of patients with ESKD on chronic haemodialysis (CHD), survival rates have been increasing, with a consequently growing prevalent population on dialysis[3]. Meanwhile, significant advances have been made in cancer care, so that even when cure is not possible, many cancers can be controlled and managed for long periods of time, making cancer a chronic condition[4].

Thus, as an increasing number of elderly patients on CHD are expected to develop cancer as a result of aging[5] and, as a consequence of a higher prevalence of cancer survivors overall, the latter are receiving treatment for

comorbidities, including chronic kidney disease. In addition, patients on CHD already have a higher risk of developing cancer independently of age[6], while oncology patients are particularly prone to developing kidney failure, as a result of the disease or its treatment[7,8].

Taken together, the combination of cancer and ESKD is an emerging issue in developed countries. Given the dismal prognosis of both entities, nephrologists and oncologists are expected to take challenging decisions regarding renal replacement therapy (starting with the question of whether to initiate treatment or not) and palliative care. However, at present, very little is known about the behaviour and outcome of this particular subset of patients on dialysis.

With the aim of improving the quality end-of-life care of patients with both cancer and ESKD, the present study characterized the clinical progression and evaluated the outcome of these patients in an attempt to identify parameters associated with prolonged survival that might aid in clinical decision-making.

SUBJECTS AND METHODS

Design and Data collection

We carried out a retrospective analysis of all patients on a chronic dialysis programme in a single oncology hospital-based haemodialysis center (Instituto Português de Oncologia do Porto, Portugal) between January 1991 and September 2014.

Patients defined as being on a chronic dialysis programme included outpatients on dialysis for more than one month.

The decision to initiate dialysis was taken by the hospital nephrologists, usually as a result of a multidisciplinary decision shared with the attending oncologists. This was, however, a subjective judgment made on a case-by-case basis, which took into consideration patients' performance status and predicted quality of life. The stability of the underlying malignancy was of major importance for the verdict. Metastatic disease did not exclude patients from CHD, except if associated with a terminal disease stage.

The collected data included general demographic aspects, such as gender and age, comorbidities (diabetes and hypertension), cause of renal failure, tumour type, presence of metastasis, time on dialysis and outcome (death, transferred to another centre, transplanted or alive on dialysis at the end of the study).

Approval to conduct this study was granted by the Ethics Committee (Comissão de Ética para a Saúde) of Instituto Português de Oncologia do Porto, Portugal.

Statistical Analysis

All analyses were carried out using the Statistical Package for Social Sciences version 22.0 for Windows and R Software version 3.1.0. Overall survival was defined from the time point at which dialysis was started until death from any cause or last known contact. Patients still alive were censored at last follow-up date. Continuous variables were expressed as the median with interquartile range (IQR), and categorical variables were expressed as absolute (*N*) and relative (%) frequencies. For subsequent analyses, continuous variables were categorized.

Differences in demographic and clinical characteristics among groups were tested using the Chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U-test for continuous variables. Bonferroni's correction was used for multiple comparisons.

Univariate and multivariate analyses were performed by a stepwise backward Cox regression model ($p<0.2$ was considered as the inclusion criterion for factors that could be added into multivariate analysis). As treatment or diagnostic innovations that can change the survival probability can occur during the follow-up period, we also included a variable in the Cox regression model corresponding to the decade of the patients' entry into the study. Hazard ratios are presented together with the 95% confidence intervals (95% CIs). The proportional hazards assumption was checked visually using Schoenfeld residuals. Significance was set at $p\leq0.05$.

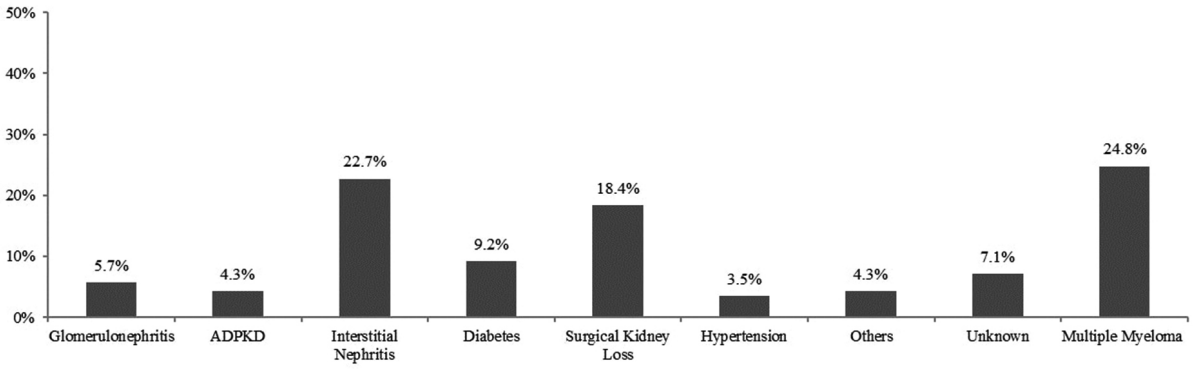
RESULTS

Causes of kidney disease

This study was conducted into 141 consecutive patients with a diagnosis of ESKD and cancer, which in most cases was locally advanced or metastatic, that underwent CHD between 1991 and 2014 at our dialysis centre.

Figure 1

Causes of kidney failure



ADPKD – autosomal dominant polycystic kidney disease

Figure 1 illustrates the main causes of kidney disease, which included, as most frequent, multiple myeloma (MM) (35; 24.8%) and chronic interstitial nephritis (34; 24.1%), followed by surgical removal of kidney (29; 20.6%).

■ Patients' clinical characterization

Table 1 shows demographic and clinical characteristics of the patients, stratified by tumour type. The most common tumours were genitourinary cancer (47.5%) and MM (24.8%) followed by breast (10.6%) and gastrointestinal (8.5%) cancers. Multiple tumours were found in 22.0% of cases. Patients with genitourinary cancer were particularly susceptible, with almost one third (31.3%) with multiple coexistent tumours.

A significant association between tumour type and gender (p=0.001) was depicted, as breast cancers were significantly less prevalent in male patients, as expected. Finally, radiation enteritis/cystitis was significantly

Table 1

Demographic and clinical characteristics of oncology patients stratified by tumour type

Characteristics	Breast	Genitourinary	MM	GI	Others	*P* value
	N (%)					
Gender						
Female	15 (100.0)[a]	28 (41.8)[b]	20 (51.7)[b]	5 (41.7)[b]	7 (58.3)[b]	0.001
Male	0 (0.0)[a]	39 (58.2)[b]	15 (42.9)[b]	7 (58.3)[b]	5 (41.7)[b]	
Age						
56	0 (0.0)	16 (23.9)	7 (20.0)	2 (16.7)	4 (33.3)	0.600
57-68	5 (33.3)	18 (26.9)	10 (28.6)	2 (16.7)	1 (8-3)	
69-75	5 (33.3)	19 (28.4)	9 (25.7)	3 (25.0)	4 (33.3)	
>75	5 (33.3)	14 (20.9)	9 (25.7)	5 (41.7)	3 (25.0)	
Multiple Tumours						
No	12 (80.0)[a,b]	46 (68.7)[b]	33 (94.3)[a]	9 (75.0)[a,b]	10 (83.3)[a,b]	0.035
Yes	3 (20.0)[a,b]	21 (31.3)[b]	2 (5.7)[a]	3 (25.0)[a,b]	2 (16.7)[a,b]	
Enteritis/Cystitis						
No	15 (100.0)[a,b]	37 (69.8)[b]	30 (100.0)[a]	7 (77.8)[a,b]	9 (100.0)[a,b]	<0.001
Yes	0 (0.0)[a,b]	16 (30.2)[b]	0 (0.0)[a]	2 (22.2)[a,b]	0 (0.0)[a,b]	
Metastasis						
No	12 (92.3)	53 (81.5)	–	9 (81.8)	6 (60.0)	0.324
Yes	1 (7.7)	12 (18.5)	–	2 (18.2)	4 (40.0)	
Total	15 (10.6)	67 (47.5)	35 (24.8)	12 (8.5)	12 (8.5)	

Different letters a,b indicate significant differences between tumour type in each category group

MM – multiple myeloma; GI – gastrointestinal

more prevalent in patients with genitourinary cancer (30.2%) (p<0.001), as result of its specific therapeutic strategy.

■ Patients' baseline characteristics

Table 2 presents the baseline demographic and clinical characteristics of the 141 patients at the start of dialysis treatment. The patients' age ranged from 20 to 89 years (median=69; IQR=58-76); and 75 (53.2%) of them were female. Almost a fifth of the patients (19; 19.2%) had metastatic cancer. The median time on dialysis was 23.6 months (IQR, 9.2-49.4).

■ Patients' survival and outcomes

After a median follow-up of 23.6 (IQR: 9.1-49.6) months, 66.7% patients were deceased;, 7.8% were transferred to other centres as a result of clinical stability; 4.3% (all of them with MM) recovered renal function; 1.4% received a kidney transplant and 19.9% were still alive at the end of the study. Globally, survival rates were 58.8% at 2 years and 34.8% at 5 years.

Table 3 shows a Cox proportional hazards regression analysis for progression to death. In univariate analysis, tumour type, gender, age and cause of kidney failure had a p<0.20 on overall survival and were included in the multivariate analysis. In contrast, the presence of metastasis, multiple tumours and the year at the beginning of dialysis were not associated with overall survival. Finally, the covariates gender and cause of kidney failure were excluded by the backward selection procedure. According to multivariable analysis, significant predictors of overall survival were tumour type and age. MM (HR=5.950; 95% CI: 2.512-14.092) and gastrointestinal cancers (HR=3.277; 95% CI: 1.176-9.134) were associated with increased likelihood of death. Furthermore, patients between 57 and 68 years old (HR=2.1; 95% CI: 1.003-4.292); between 69 and 75 (HR=2.720; 95% CI: 1.352-5.473) or over 75 years old (HR=3.118; 95% CI: 1.500-6.480) were at increased risk of dying compared with patients 56 years old or younger.

Table 2

Baseline characteristics of the participants at the start of dialysis

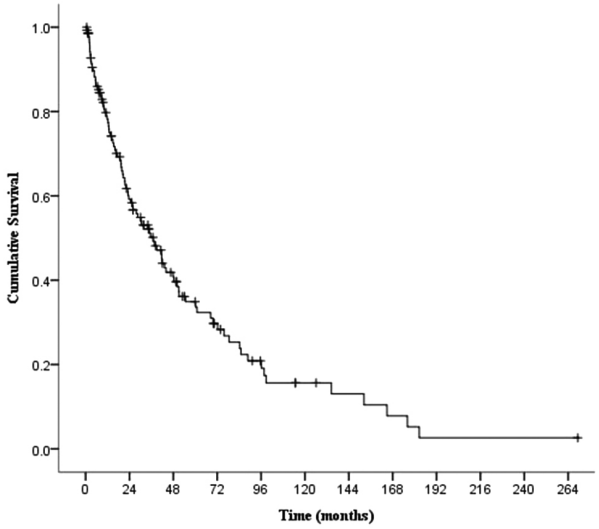
Characteristics	Patients
Age at the beginning of dialysis, median, in years (p25-p75)	69 (58-76)
Age groups	
<=56	29 (20.6)
57-68	36 (25.5)
69-75	40 (28.4)
>=76	36 (25.5)
Gender	
Females	75 (53.2)
Males	66 (46.8)
DM 2	
No	89 (74.8)
Yes	30 (25.2)
Hypertension	
No	60 (50.4)
Yes	59 (49.6)
Time on dialysis, median, in months (p25-p75)	23.6 (9.2-49.4)
Metastasis	
No	80 (80.8)
Yes	19 (19.2)

[a] Numbers in parentheses refers to N (%), unless otherwise specified

ADPKD – autosomal dominant polycystic kidney disease; DM 2 – Diabetes mellitus type 2

Figure 2

Overall survival



The causes of death were not possible to determine in 13 out of 94 patients. Of the remaining 81 patients, 64.2% died of tumour progression; 19.8% of cardiovascular events; 4.9% of infection; 8.6% of other causes and 2 patients died of unknown cause.

■ DISCUSSION

As a result of new therapeutic strategies and improved patient care, there is a growing prevalence of cancer survivors and patients with ESKD on CHD.

Table 3

Potential risk factors for mortality

Variable	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Tumour Type				
Breast	Ref		Ref	
Genitourinary	1.353 (0.636;2.879)	0.433	1.346 (0.588;3.080)	0.482
MM	5.590 (2.429;12.865)	<0.001	5.950 (2.512;14.092)	<0.001
Gastrointestinal	3.577 (1.378;9.287)	0.009	3.277 (1.176;9.134)	0.023
Others	1.877 (0.644;5.472)	0.249	2.645 80.847;8.256)	0.094
Gender				
Female	Ref.		–	
Male	1.504 (1.000;2.262)	0.050		
Age				
<=56	Ref.		Ref	
57-68	1.816 (0.909;3.628)	0.091	2.074 (1.003,4.292)	0.049
69-75	2.455 (1.247;4.834)	0.009	2.720 (1.352;5.473)	0.005
>=76	2.984 (1.495;5.958)	0.002	3.118 (1.500;6.480)	0.002
Metastasis				
No	Ref		–	
Yes	0.989 (0.513;1.904)	0.973		
Multiple tumours				
No	Ref		–	
Yes	0.829 (0.513;1.340)	0.444		
Cause of kidney failure				
Hypertension	Ref		–	
Glomerulopathy	4.035(0.834;19.522)	0.083		
ADPKD	1.153(0.191;6.973)	0.877		
Chronic interstitial nephritis	2.566(0.605;10.877)	0.201		
Diabetes	2.812(0.579;13.655)	0.200		
Surgical kidney loss	1.192(0.268;5.314)	0.818		
Others	5.108(0.914;28.537)	0.063		
Unknown	3.602(0.717;18.093)	0.120		
MM	7.822(1.809;33.825)	0.006		
Beginning of dialysis				
1990-1999	0.719 (0.355;1.458)			
2000-2009	1.210 (0.685;2.138)	0.360		
2010-2014	Ref	0.511	–	

ADPKD – autosomal dominant polycystic kidney disease; MM – multiple myeloma

Both entities are associated with decreased survival, when compared to the general population[1,2] and both represent in themselves a risk factor for each other[9-11]. Consequently, it is crucial firstly to recognize the complex relationship between malignancies and chronic renal failure, and secondly to assess each's impact on the other's course of events.

There is, however, a paucity of information concerning the clinical progress and outcomes of oncology patients on chronic dialysis. Thus, our study aimed to characterize a group of oncology patients on CHD followed at a dialysis centre in an oncology hospital. This is, to the authors' knowledge, the first report specifically dealing with a group of cancer patients on chronic dialysis for an extended period of time.

In our study, the most common cancers were in the genitourinary system, followed by MM. The former leads to renal impairment mainly through two different mechanisms: either by the development of chronic interstitial nephritis related to urinary tract obstruction[12] or surgical kidney loss as a result of treatment strategies[13]. Enteritis and haemorrhagic cystitis as *sequelae* of radiotherapy were often found in these patients and frequently coexisted. MM, on the other hand, was the second most prevalent tumour and the first cause of ESKD, mainly as a result of cast nephropathy.

In our dataset, 22% of the patients displayed multiple tumours and these were more common among patients with genitourinary cancer, which may be, at least

partially, explained by the multifocal nature of transitional cell carcinoma of the urothelium[14,15].

Two patients were considered cured and received a kidney transplant. One was a 62-year-old woman with ovarian cancer and a pheochromocytoma, transplanted after 38 months on dialysis. The other was a woman with an ovarian germ cell tumour who had a first failed renal transplantation at the age of 26 and was finally transplanted with success at age 28 years, after 31 months on dialysis.

Despite the prevalence of MM as a cause of renal injury and its dismal prognosis, patients with MM, were, however, the only subset in which recovery of renal function was observed, as previously reported[16,17]. The patient who recovered more rapidly was on dialysis for 6 weeks and the one who remained longer on CHD was off haemodialysis after 14 months.

Tumour type was associated with risk of death, with MM and gastrointestinal cancers showing the worst prognosis. This distribution matches that of published reports[18] on cancer survival. Interestingly, patients with metastatic disease were not associated with worse survival, probably due to the fact that patients who had metastasis were only admitted for chronic dialysis if considered stable and at low risk of progression in the short-term. Conversely, some patients without metastasis had locally advanced and aggressive tumours, hence not always corresponding to a better prognosis in comparison to those with disseminated disease.

Although, on the one hand, patients treated over the last decade had better treatment options and presumably a better prognosis; on the other hand, patients that began dialysis in our centre more recently have, in general, more comorbidities. Because we are able to provide a better care, many of the patients that are now proposed for CHD would not have even been considered for dialysis two decades ago, including, for instance, many patients with MM. This might explain the lack of statistically significant difference in survival among patients that were treated in 1991 or 2014.

Surprisingly, more than half the patients were still alive after 2 years on haemodialysis and more than one third after 5 years. Most of them died of causes related to the oncological disease, such as complications of chemo- or radiotherapy and progressive anorexia and frailty. Interestingly, if we consider that 5-year survival for patients on chronic haemodialysis ranges from 39.8% to 37.2% for diabetic patients[19], our data are similar to those described for this subgroup of non-oncology patients.

Our results highlight the importance of considering these patients for renal support therapies, demonstrating that a large number of patients might benefit from CHD in spite of the unfavourable prognosis of concomitant cancer and ESKD. There is, however, the need to follow these patients closely and continuously assess their quality of life so that we may offer adequate palliative care, when justified. For that purpose, our unit works in close collaboration with the palliative care team. Patients with disease progression and/or severe decline in quality of life interrupted dialysis after multidisciplinary discussion. If needed, patients were treated with ultrafiltration on an on-demand basis for the relief of dyspnoea.

We could not compare the outcomes of our patient population with other studies, since previous reports usually focused on either patients with renal failure who develop cancer[6,20-21] or cancer patients with acute kidney disease[22-24]. Launay-Vacher et al. has largely contributed to highlighting the risk of renal disease (acute and chronic) in cancer patients[25,26], but no data is available for cancer patients on CHD.

There are some limitations to the current study that should be highlighted. Firstly, this is a cohort from a single centre without external validation and, as previously addressed, there may be some bias in the selection of patients for haemodialysis. Secondly, as a retrospective study, patients were not randomly assigned to haemodialysis and selection for CHD was subjective, according to the medical team that assisted the patient. However, a prospective study regarding this matter would most probably prove unethical. Third, there is the potential for an era-effect. The time period under study was long and spans a time of change in therapy. To minimize this, we split the group into time periods to compare the outcomes, but no statistically significant differences were disclosed.

CONCLUSION

The paucity of data on cancer patients with concomitant ESKD on CHD makes decisions on whether to initiate or withdraw haemodialysis, as well as prescription of specific cancer therapies, controversial. We believe that this study sheds a new light on the

prognosis of this particular population and indicates that a sizeable proportion of these patients may expect a long survival on CHD.

More studies are, however, required to help support clinicians often facing very complex ethical issues. Studies on quality of life might also usefully explore this matter.

Disclosure of potential conflicts of interest: none declared

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