Potrebbe l'emodialisi incrementale essere un nuovo standard di cura? Un suggerimento da uno studio osservazionale a lungo termine

Articoli Originali

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ABSTRACT

Introduzione: Il termine emodialisi (HD) incrementale significa che sia la dose di dialisi che la frequenza possono essere piccole all'inizio del trattamento dialitico e dovrebbero essere aumentate progressivamente per compensare una successiva riduzione della funzione renale residua. Politica del Centro Dialisi di Matera è tentare un inizio incrementale del trattamento dialitico senza una rigorosa dieta ipoproteica in tutti i pazienti che scelgono l'HD e con diuresis quotidiana (UO) >500 ml/die. Questo studio ha lo scopo di analizzare i risultati di questa politica negli ultimi 20 anni.

Materiali e metodi: Sono stati valutati i dati dei pazienti che hanno iniziato il trattamento dialitico nel periodo compreso tra il 01-01-2000 e il 31-12-2019. Criteri di esclusione dallo studio furono: diuresi giornaliera <500 ml/die o follow-up <3 mesi dopo l'inizio del trattamento dialitico.

Risultati: I pazienti valutati furono 266; 64 furono esclusi dallo studio. I restanti 202 pazienti furono arruolati nello studio e suddivisi in 3 gruppi (G1, G2 e G3) in base alla frequenza del trattamento all'inizio della dialisi: 117 pazienti (57.9%) cominciarono con ritmo monosettimanale (1HD/wk) (G1); 46 (22.8%) con ritmo bisettimanale (2HD/wk) (G2); 39 (19.3%) con ritmo trisettimanale (3HD/wk) (G3). I pazienti di G1 rimasero in 1HD/wk 11.9 ±14.8 mesi e furono successivamente trasferiti in 2HD/wk per ulteriori 13.0 ±20.3 mesi. I pazienti di G2 rimasero in 2HD/wk 16.7 ±23.2 mesi. Complessivamente, 25943 sessioni furono effettuate durante i periodi di dialisi meno frequente invece di 47988, che sarebbero state effettuate se i pazienti fossero state trattati con 3HD/wk, risparmiando così 22045 sedute (45.9%). La mortalità dell'intero gruppo fu 12.6%, sovrapponibile a quella della mortalità media della popolazione dialitica italiana (16.2%). La sopravvivenza a 1 e 5 anni, non differente in maniera significativa tra i 3 gruppi, fu: 94% e 61% (G1); 83% e 39% (G2); 84% e 46% (G3).

Conclusioni: Il nostro studio osservazionale a lungo termine suggerisce che l'HD incrementale è una valida opzione nei pazienti incidenti, essendo possibile nella gran parte di loro (80.7%) per circa 1-2 anni, con evidenti benefici socio-economici e percentuali di sopravvivenza comparabili a quelli della popolazione dialitica italiana. Tuttavia, mancano studi randomizzati controllati e quindi necessari urgentemente. Se questi confermeranno i dati osservazionali, l'HD incrementale sarà un nuovo standard di cura.

PAROLE CHIAVE: emodialisi, emodialisi incrementale, clearance renale dell'urea, modello cinetico dell'urea, Diuresi

Introduction

There is growing interest in an incremental approach to haemodialysis (HD) for incident end-stage kidney disease (ESKD) patients, starting with one (1HD/wk) or two sessions per week (2HD/wk) [1–4]. Such an approach not only seems to preserve residual kidney function (RKF) and improve health-related quality of life with similar or higher survival rates than those observed in patients receiving the standard thrice weekly HD (3HD/wk) regimen, but also allows saving economic resources [5–7]. The term "incremental HD" means that, in the presence of substantial RKF, both dialysis dose and frequency can be low at dialysis inception but should be progressively increased, to compensate for any subsequent reduction in RKF [8, 9].

RKF in dialysis patients plays important roles in fluid and salt removal, effective phosphorus excretion, middle molecule clearance, and endogenous vitamin D and erythropoietin production [1, 2]. There is increasing evidence to suggest that clearance of some uraemic solutes, particularly middle molecules such as β_2-microglobulin, is highly dependent on RKF. This extends even to very low levels of RKF: patients with kidney urea clearance (KRU) <0.5 ml/min have significantly higher serum β_2-microglobulin levels than those with values between 0.5 and 1 ml/min [10]. Furthermore, residual renal tubular function may represent important removal pathways for these and other compounds, such as hippurate, phenylacetylglutamine, indoxyl sulfate, and p-cresol sulfate [11, 12].

Loss of RKF is linked to decreased survival [13, 14], likely from poorer uraemic solute clearance [13], volume and blood pressure control [15, 16], higher erythropoietin requirements [17], more inflammation [13] and higher left ventricular mass [18]. The benefits of preserving KRU appear to be greater that one would expect from simply enhanced small solute clearance: a multivariate survival analysis of patients on incremental HD suggested that 1 ml/min of KRU resulted in greater survival benefit compared to 1 ml/min of dialysis urea clearance, possibly due to greater removal of middle molecules by native kidneys and improved volume control [15]. Finally, the available literature suggests greater preservation of RKF with infrequent dialysis [5, 7, 19].

The Matera Dialysis Center has adopted over the last 20 years the policy of attempting to start HD always incrementally in all ESKD patients in relatively stable conditions and with preserved diuresis. Over the years, a lot of data has accumulated on patients who received incremental HD in our Center. The present study aims to compare the long-term results of such a policy.

Subjects and methods

Policy of the Matera Dialysis Center

As mentioned above, the policy of our Center over the last 20 years has been to try to initiate HD incrementally in almost all patients with advanced chronic kidney disease (CKD-5D), in relatively stable conditions and with preserved diuresis. All patients treated in our Center give their written informed consent to the choice of HD as first mode of renal replacement therapy (RRT); furthermore, they give written informed consent to starting with the incremental regimen. They also receive the information that a less frequent treatment can be harmful, especially in the presence of insufficient RKF. Two important corollaries complete this information:

1. the need of collecting periodically the 24-hour urine output (UO) to quantify RKF;
2. the need of promptly increasing dialysis frequency if RKF falls below established levels, even in the absence of clear symptoms and signs of clinical worsening.

In brief, the dialysis treatment is started with 1 or 2 sessions per week and can be empirically increased to 2 or 3, based on the trend of clinical and biochemical data, with particular regard to the state of nutrition, the values of KRU, dialysis dose (Kt/V) and normalized protein catabolic rate (PCRn), which are assessed monthly.

Inclusion/exclusion criteria

For decades, all the main clinical, biochemical and epidemiological data of patients treated at the Hospital of Matera's Division of Nephrology, have been managed and archived with the GEPADIAL® software (La Traccia, Matera, Italy). This allowed us to retrieve the dataset of all patients who had started HD in the Matera Dialysis Center from January 1st, 2000 to December 31st, 2019 (with a prolongation of the follow-up until June 30th, 2021). In particular, for each patient, the duration of the follow-up was calculated from the difference (in months) between the date of the first and last dialysis session in our Center.

Patients who had a follow-up <3 months after the start of the dialysis treatment were excluded from the study to avoid enrolling patients affected by acute kidney injury, or severely sick, or transiently treated in our Center. Patients with a follow-up >3 months but with UO <500 ml/day at the start of treatment were also excluded from the study. Patients were divided into three groups (G), which were determined exclusively by the weekly regimen at the start of dialysis treatment: G1: once-a-week (1HD/wk); G2: twice-a-week (2HD/wk); G3: thrice-a-week (3HD/wk), and regardless of subsequent rhythm variations, if any, thus creating a kind of intervention arm of an "intention to treat" study, taking into account the policy of our Center, i.e., that of trying to initiate HD incrementally in almost all patients.

Measurement of the main parameters of UKM

The measurement of the main parameters of urea kinetic modeling (UKM) (Kt/V, PCRn and KRU if UO >200 ml/day) was performed on a monthly basis in all patients, using the specific software GEPADIAL®, based on the so-called modified algorithm of UKM [20]. The software automatically calculates also the "equivalent renal urea clearance" (EKR) corrected for a urea distribution volume of 40 l (EKRc) [21]. The latter has been converted into the new version of EKR, which is corrected for a urea distribution volume of 35 l with the following formula: EKR35 = EKRc x 35/40 [22]. The calculation of the post-rebound equilibrated Kt/V (eKt/V) and of the most recent version of the standardized Kt/V (stdKt/V) has been utilized in the present study using the formulas recommended by the KDOQI Clinical Practice Guideline for Hemodialysis Adequacy 2015 [9]. Furthermore, the latter proposed the following criteria of adequacy of stdKt/V: a target value of 2.3 and a minimum value of 2.1 volumes/week (v/wk) for non-thrice-a-week dialysis rhythms [9]. Similarly, Casino and Basile have proposed the following criteria of adequacy of EKR35: a target and a minimum value, as described by the following equations:

1. target EKR35 = 12 – KRUN (EKRT12) [22, 23]
2. minimum EKR35 = 10 – 1.5 x KRUN (EKRT10) [23, 24]

where KRUN = KRU (ml/min)/V (l) x 35 (l) [23].

Two sets of kinetic data were obtained for each patient, at two different time points of the treatment. The first one (T3), corresponding to approximately 3 months of dialysis, coincides with the third measurement of the main parameters of UKM, and should reflect the initial, but already fairly stabilized, stage of treatment; the second one (T_end) changes from one patient to another: it corresponds to the time point at which a last value of UO >200 ml/day was available during the study, or just before the exit of the patient from the study because of death, kidney transplant, transfer to another center or end of the study (June 30th, 2021), the patient being alive.

Statistics

Means and standard deviations (SD) were obtained using Excel®; χ^2 test, graphics, Student's t-test, ONE-WAY ANOVA and survival analyses (Kaplan-Meier) were performed with the statistical package R of CRAN project [25–27].

Results

Data related to 266 patients were retrieved from the local electronic database, representing the set of all patients who started maintenance HD at the Matera Dialysis Center in the study period considered: of them, 45 (17%) were excluded because their follow-up after the start of the dialysis treatment was <3 months; 12 (4%) were excluded because they had started the dialysis treatment in the setting of continuous renal replacement therapy; lastly, 7 (3%) were excluded because their baseline UO was either <500 ml/day or had not been reported. All in all, 202 patients were enrolled into the study. The main demographic, clinical and laboratory data of the 202 patients enrolled into the study are reported in Table I.

They were subdivided into 3 groups (G), according to their weekly regimen at the start of dialysis treatment: 117 were on a once-a-week (G1), 46 on a twice-a-week (G2), and 39 on a thrice-a-week schedule (G3).

Age (years)	66 ±15		**Serum albumin (g/l)**	29.7±11.7
Gender (male/female)	120/82		**Diabetic nephropathy**	42 (20.8 %)
Body weight (kg)	63.2 ±13.3		**Glomerulonephritis**	40 (19.8%)
Body mass index (kg/m^2)	24.6 ±4.4		**Hypertensive nephropathy**	52 (25.7%)
Body surface area (m^2)	1.65 ±0.197		**Interstitial nephropathy**	29 (14.4%)
Blood urea nitrogen (mg/dl)	99 ±33		**Polycystic kidney disease**	9 (4.5%)
Serum creatinine (mg/dl)	8.0 ±3.1		**Other/Unknown**	30 (14.9%)
KRU (ml/min/1.73 m^2)	4.5 ±1.6		**Charlson comorbidity index**	6.9 ±2.6
ClCr (ml/min/1.73 m^2)	8.0 ±2.9		**Late referral (<3 months)**	33 (16.3%)
GFRm (ml/min/1.73 m^2)	6.2 ±2.1		**Group 1 (G1): start on 1HD/wk**	117 (57.9%)
Urine Output (ml/day)	1800 ±700		**Group 2 (G2): start on 2HD/wk**	46 (22.8%)
Proteinuria (g/day)	3.0 ±3.0		**Group 3 (G3): start on 3HD/wk**	39 (19.3%)

Table I: It reports the main demographic, clinical and laboratory data of the 202 patients enrolled into the study. Means ±SD; KRU = residual kidney urea clearance; ClCr = creatinine clearance; GFRm = mean of KRU and ClCr.

Table II shows the comparison of the main demographic, clinical and laboratory data between the groups of patients starting HD incrementally (G1+G2) and the group of patients starting dialysis on a thrice-a-week schedule (G3). KRU and UO were significantly lower in G3; this group had a percentage of women and late referral to the nephrology team (follow-up <3 months before the start of the dialysis treatment) much larger than G1+G2 (61.5% *vs*. 35.6%, P = 0.003; 38.5% *vs.* 11.0%, P = 0.001, respectively).

Figure 1 shows the numbers of patients on 1HD/wk, 2HD/wk and 3HD/wk at different time points: at the start (T0) and 3 (T3), 12 (T12), 24 (T24) and 60 (T60) months after the start of dialysis treatment: 94 patients (46.5%) and 52 patients (25.7%) were on incremental HD after 1 and 2 years, respectively.

	G1+G2 (N = 163)	G3 (N = 39)	t	P
Gender (M/F) (%)	105/58 (F=35.6%)	15/24 (F=61.5%)	8.79*	0.003
Age (years)	66.91 ±14.63	62.15 ±16.96	1.769	0.078
Body weight (kg)	63.43 ±13.37	62.09 ±12.96	0.568	0.571
Body mass index (kg/m^2)	24.7 ±4.47	24.38 ±4.15	0.400	0.689
Diabetic nephropathy	32	10		
Glomerulonephritis	31	9		
Hypertensive nephropathy	46	6	4.48*	0.482
Interstitial nephropathy	25	4		
Polycystic kidney disease	7	2		
Other/Unknown	22	8		
Blood urea nitrogen (mg/dl)	98.30 ±29.96	100.38 ±43.66	-0.354	0.724
Serum creatinine (mg/dl)	7.87 ±2.65	8.70 ±4.61	-1.482	0.14
Serum albumin (g/l)	30.22 ±11.90	27.36 ±10.51	1.377	0.170
Urine Output (ml/day)	1875 ±659	1357 ±816	4.195	<0.001
Proteinuria (g/day)	2.95 ±2.90	3.35 ±3.57	-0.746	0.456
KRU (ml/min/1.73 m^2)	4.63 ±1.42	3.76 ±1.94	3.195	0.002
ClCr (ml/min/1.73 m^2)	8.10 ±2.42	7.60 ±4.52	0.951	0.343
GFRm (ml/min/1.73 m^2)	6.36 ±1.79	5.68 ±3.05	1.836	0.068
Late referral (<3 months) (%)	18/163 (11.0%)	15/39 (38.5%)	17.3*	0.001
Charlson comorbidity index	6.99 ±2.64	6.51 ±2.63	1.011	0.313

Table II: Comparison of the main demographic, clinical and laboratory data between the groups of patients starting HD incrementally (G1+G2) and the group of patients starting dialysis on a thrice-a-week schedule (G3). Means ±SD; KRU = residual kidney urea clearance; ClCr = creatinine clearance; GFRm = mean of KRU and ClCr. All the variables of the 2 groups were compared with the Student's t-test, except gender, classes of nephropathies and late referral, which were compared with the c2 test (*).

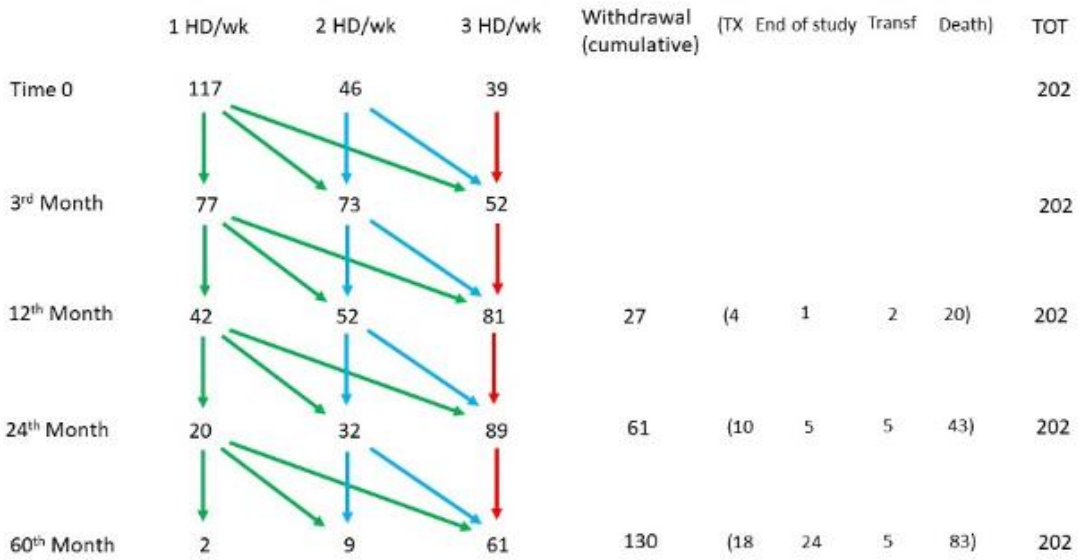


Figure 1: It shows the numbers of patients on 1HD/wk, 2HD/wk and 3HD/wk at different time points: at the start (T0), and 3 (T3), 12 (T12), 24 (T24) and 60 (T60) months after the start of dialysis treatment: 94 patients (46.5%) and 52 patients (25.7%) were on incremental HD after 1 and 2 years, respectively.

Table III shows the main clinical data including kinetic studies of the entire population under study and of the 3 groups of patients at the third month of dialysis treatment (T3).

Notably, UO and KRU were significantly higher in G1 and G2 than in G3, whereas PCRn, EKR35 and stdKt/V were significantly lower in G1 and progressively increased in G2 and G3.

Table IV shows the main clinical data including kinetic studies of the entire population under study and of the 3 groups of patients at T_end. It occurred 27.9 ±27.6 months after the start of dialysis treatment. The main significant differences among the three groups were the number of dialysis sessions per week, UO, weekly UF, EKR35 and stdKt/V.

Table V shows the differences among the values of the main clinical data including kinetic studies at T3 and T_end (data of the entire population under study and of the 3 groups of patients).

The main differences were: a net reduction in KRU and UO, an increase in the number of weekly sessions, weekly ultrafiltration, EKR35 and stdKt/V.

Groups of patients (N)	Total (202)	G1 (117)	G2 (46)	G3 (39)	p*
BUN-pre (mg/dl)	79.3 ±24.4	84.5 ±23.7	73.9 ±22.1	70.0 ±25.4	0.002
BUN-post (mg/dl)	25.1 ±13.4	27.0 ±14.6	23.7 ±11.4	20.9 ±10.8	0.021
Session length (min)	228 ±21.7	228 ±21.4	230 ±20.8	225 ±223.8	0.708
Sessions per week (n/wk)	1.88 ±0.79	1.41 ±0.60	2.13 ±0.34	3.00	
Body weight-pre (kg)	64.8 ±13.5	63.9 ±12.6	67.5 ±15.9	64.2 ±13.0	0.392
Body weight-post (kg)	63.1 ±13.3	62.5 ±12.4	65.5 ±15.6	62.3 ±12.8	0.466
Ultrafiltration (l/session)	1.68 ±0.99	1.47 ±0.95	1.99 ±1.13	1.96 ±0.77	0.002
Weekly ultrafiltration (l/week)	3.24 ±2.37	2.24 ±1.90	4.63 ±2.65	4.58 ±1.79	0.001
Urine Output (ml/day)	1380 ±690	1547 ±660	1374 ±724	900 ±493	0.001
KRU (ml/min/1.73 m^2)	3.34 ±1.79	3.54 ±1.74	3.50 ±1.89	2.53 ±1.63	0.005
Single pool Kt/V	1.40 ±0.40	1.38 ±0.41	1.41 ±0.37	1.47 ±0.36	0.427
Equilibrated Kt/V	1.24 ±0.35	1.22 ±0.37	1.24 ±0.33	1.29 ±0.32	0.452
PCRn (g/kg/day)	1.05 ±0.30	0.99 ±0.25	1.13 ±0.30	1.15 ±0.39	0.006
EKR35 (ml/min/35 l)	10.8 ±3.62	9.2 ±3.1	11.9 ±2.7	14.4 ±2.8	0.001
Standard Kt/V (v/wk)	2.45 ±0.74	2.14 ±0.65	2.67 ±0.60	3.12 ±0.62	0.001

Table III: Main clinical data including kinetic studies of the entire population under study and of the 3 groups of patients at the third month (T3). Means ±SD; *ONE-WAY ANOVA; BUN = Blood urea nitrogen; KRU = residual kidney urea clearance; PCRn = normalized protein catabolic rate; EKR35 = Equivalent renal urea clearance (EKR) corrected for urea distribution volume of 35 l.

Figure 2 shows that 50 out of 76 (66%) patients on 1HD/wk would have been considered receiving inadequate total weekly clearances at T3, by applying the minimum value of stdKt/V [9]. Figure 3 shows that only 15 out of 76 (19.7%) patients on 1HD/wk would have been considered receiving inadequate total weekly clearances at T3, by applying the minimum value of EKR35 [23, 24]. Figure 4 shows the curves of survival (Kaplan-Meier analysis) of RKF, expressed as time to event referred to the first observation of UO $\leq$200 ml/day, in the three groups of patients. The median estimates (months) were: G1 40.3; G2 23.2; G3 26.5. The differences were statistically significant when comparing G1 with G2, and G1 with G3, but not when comparing G2 with G3.

Groups of patients (N)	Total (202)	G1 (117)	G2 (46)	G3 (39)	p*
BUN-pre (mg/dl)	76.2 ±22.2	78.2 ±22.5	80.2 ±22.4	65.8 ±18.3	0.001
BUN-post (mg/dl)	21.0 ±8.9	21.4 ±8.8	23.2 ±9.6	17.2 ±16.8	0.002
Session length (min)	231 ±19.0	230 ±19.9	234 ±13.5	230.±21.9	0.353
Sessions per week (n/wk)	1.97 ±0.79	2.17 ±0.89	2.60 ±0.55	2.90 ±0.36	<0.001
Body weight-pre (kg)	63.7 ±13.6	62.6 ±12.6	66.4 ±15.8	63.9 ±13.6	0.353
Body weight-post (kg)	61.7 ±13.2	60.7 ±12.3	64.1 ±15.3	61.7 ±13.4	0.398
Ultrafiltration (l/session)	2.07 ±1.03	1.95 ±1.06	2.3 ±1.07	2.2 ±0.84	0.036
Weekly ultrafiltration (l/week)	4.67 ±2.51	4.3 ±2.6	5.2 ±2.5	5.1 ±2.0	0.039
Urine Output (ml/day)	650 ±440	688 ±476	646 ±479	538 ±242	0.036
KRU (ml/min/1.73 m^2)	1.45 ±1.11	1.41 ±1.06	1.49 ±1.33	1.50 ±1.07	0.878
Single pool Kt/V	1.53 ±0.35	1.53 ±0.36	1.49 ±0.36	1.59 ±0.31	0.383
Equilibrated Kt/V	1.35 ±0.31	1.35 ±0.32	1.31 ±0.32	1.40 ±0.28	0.410
PCRn (g/kg/day)	1.06 ±0.32	1.01 ±0.27	1.14 ±0.31	1.09 ±0.43	0.109
EKR35 (ml/min/35 l)	11.8 ±3.27	11.1 ±3.5	11.9 ±2.5	13.5 ±2.8	0.001
Standard Kt/V (v/wk)	2.46 ±0.59	2.32 ±0.63	2.48 ±0.49	2.85 ±0.40	0.001

Table IV: Main clinical data including kinetic studies at T_end. Data of the entire population under study and of the 3 groups of patients are shown. Means ±SD; *ONE-WAY ANOVA; KRU = residual kidney urea clearance; BUN = Blood urea nitrogen; PCRn = normalized protein catabolic rate; EKR35 = Equivalent renal urea clearance (EKR) corrected for urea distribution volume of 35 l.

Groups of patients (N)	Total (202)	G1 (117)	G2 (46)	G3 (39)	p*
BUN-pre (mg/dl)	-3.05 ±27.2	-6.36 ±28.9	6.33 ±25.5	-4.2 ±21.1	0.024
BUN-post (mg/dl)	-4.10 ±13.6	-5.63 ±15.4	-0.5 ±10.6	-3.71 ±10.2	0.057
Session length (min)	2.98 ±23.3	2.0 ±24.7	4.0 ±20.0	4.8 ±23.1	0.756
Sessions per week (n/wk)	0.63 ±0.83	0.94 ±0.86	0.52 ±0.55	0.02 ±0.16	0.001
Body weight-pre (kg)	-1.07 ±4.96	-1.30 ±4.97	-1.15 ±3.31	-0.28 ±6.41	0.666
Body weight-post (kg)	-1.46 ±4.91	-1.78 ±4.97	-1.42 ±3.23	-0.53 ±6.22	0.510
Ultrafiltration (l/session)	0.39 ±1.30	0.48 ±1.36	0.28 ±1.43	0.24 ±0.92	0.430
Weekly ultrafiltration (l/week)	1.43 ±3.05	2.05 ±3.05	0.61 ±3.36	0.56 ±2.15	0.002
Urine Output (ml/day)	-0.73 ±0.75	-0.86 ±0.74	-0.73 ±0.78	-0.36 ±0.59	0.001
KRU (ml/min/1.73 m^2)	-1.9 ±1.9	-2.1 ±1.8	-2.0 ±2.0	-1.0 ±1.6	0.002
Single pool Kt/V	0.12 ±0.40	0.15 ±0.43	0.08 ±0.35	011 ±0.37	0.595
Equilibrated Kt/V	0.11 ±0.36	0.13 ±0.39	0.07 ±0.31	0.10 ±0.33	0.624
PCRn (g/kg/day)	0.01 ±0.35	0.02 ±0.31	0.02 ±0.41	-0.06±0.38	0.468
EKR35 (ml/min/35 l)	0.98 ±3.55	1.99 ±3.66	-0.02 ±2.63	-0.91 ±3.11	0.001
Standard Kt/V (v/wk)	0.01 ±0.67	0.18 ±0.71	0.52 ±0.55	-0.27 ±0.53	0.001

Table V: Differences among the values of the main clinical data including kinetic studies at T3 and T_U200. Data of the entire population under study and of the 3 groups of patients are shown. Means ±SD; *ONE-WAY ANOVA; BUN = Blood urea nitrogen; PCRn = normalized protein catabolic rate; EKR35 = Equivalent renal urea clearance (EKR) corrected for urea distribution volume of 35 l.

The duration (means ±SD) of once-a-week, twice-a-week and thrice-a-week treatments performed in the 3 groups of patients is summarized in Table VI: patients of G1 received 1HD/wk for 11.9 ±14.8 months, and subsequently 2HD/wk for further 13.0 ±20.3 months; patients of G2 received 2HD/wk for 16.7 ±23.2 months.

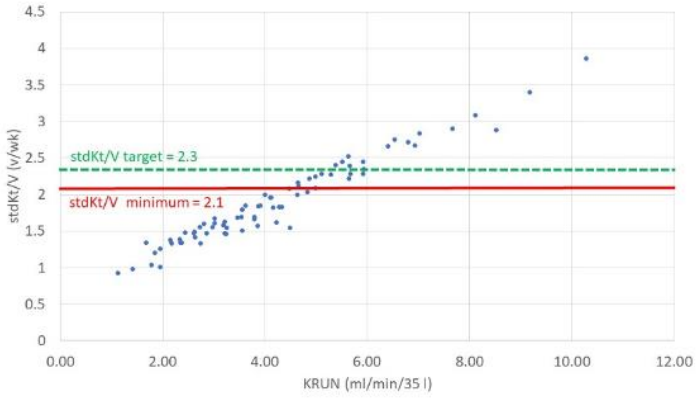


Figure 2: It shows that 50 out of 76 (66%) patients on 1HD/wk would have been considered receiving inadequate total weekly clearances at T3, by applying the minimum value of stdKt/V [9].

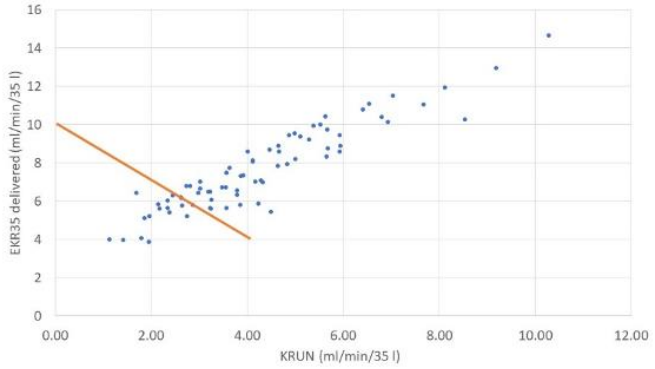
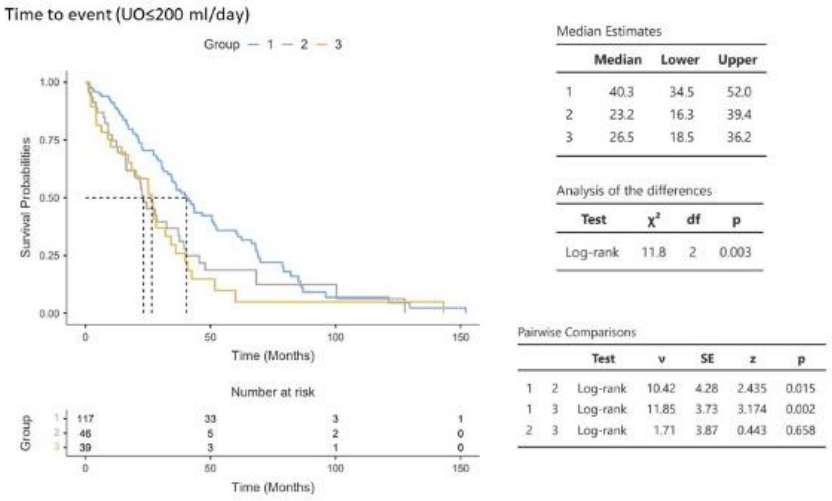


Figure 3: It shows that only 15 out of 76 (19.7%) patients on 1HD/wk would have been considered receiving inadequate total weekly clearances at T3, by applying the minimum value of EKR35 [23].



Median Estimates

	Median	Lower	Upper
1	40.3	34.5	52.0
2	23.2	16.3	39.4
3	26.5	18.5	36.2

Analysis of the differences

Test	χ^2	df	p
Log-rank	11.8	2	0.003

Pairwise Comparisons

		Test	v	SE	z	p
1	2	Log-rank	10.42	4.28	2.435	0.015
1	3	Log-rank	11.85	3.73	3.174	0.002
2	3	Log-rank	1.71	3.87	0.443	0.658

Figure 4: It shows the curves of survival (Kaplan-Meier analysis) of RKF, expressed as time to event referred to the first observation of UO <200 ml/day, in the three groups of patients. The median estimates (months) were: G1 40.3; G2 23.2; G3 26.5. The differences were statistically significant when comparing G1 with G2, and G1 with G3, but not when comparing G2 with G3.

	G1 (N=117)	G2 (N=46)	G3 (N=39)	P
Months on 1HD/wk	11.9 ±14.8	0	0	
Months on 2HD/wk	13.0 ±20.3	16.7 ±23.2	0	0.315*
Months on 3HD/wk	37.4 ±46.5	34.7 ±38.6	56.3 ±55.3	0.113**
Months of follow-up	62.6 ±48.8	51.4 ±40.8	56.3 ±55.3	0.327**

Table VI: Duration of dialysis treatments in the three groups of patients. Means ±SD; *Student's t-test; **ONE WAY ANOVA.

Patients on incremental HD (G2+G2) were administered 25943 dialysis sessions, of which 6066 on 1HD/wk and 19877 on 2HD/wk. We estimated that a total of 47988 dialysis sessions would have been administered to them if they had been on a thrice-a-week schedule for exactly the same period of time, thus saving 22045 sessions, equal to 45.9%. Just taking into account the reimbursement cost of one session of standard bicarbonate dialysis (service code 39.95.4 of the Italian Health Service, rate = 165€), approximately 3.64 million € would have been saved. Figure 5 shows the survival curve of the entire group of 202 patients estimated by means of the Kaplan-Meier analysis: the median estimate was 66 months with 95% confidence interval comprised between 54 and 84 months. Figure 6 shows the survival curves of the three groups of patients estimated by means of the Kaplan-Meier analysis at 12, 36 and 60 months of dialysis treatments: the trend was better in patients of G1 than in patients of G2 and G3; however, the difference was not statistically significant.

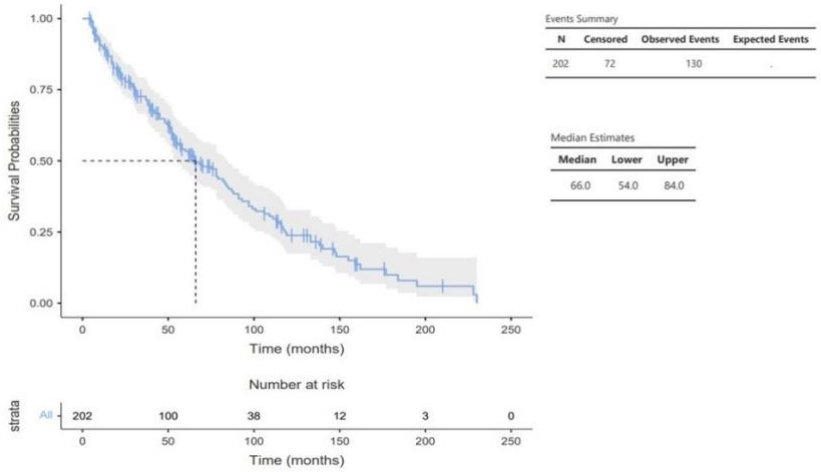


Figure 5: It shows the survival curve of the entire group of 202 patients estimated by means of the Kaplan-Meier analysis: the median estimate was 66 months with 95% confidence interval comprised between 54 and 84 months.

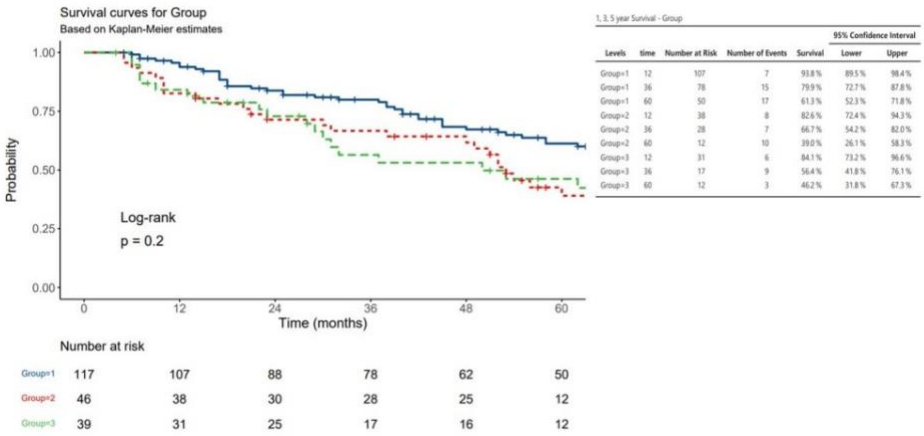


Figure 6: It shows the survival curves of the three groups of patients estimated by means of the Kaplan-Meier analysis at 12, 36 and 60 months of dialysis treatments: the trend was better in patients of G1 than in patients of G2 and G3; however, the difference was not statistically significant.

Discussion

Our study suggests that incremental HD is a valuable option in incident patients, and is viable in most of them (80.7%) for about 1-2 years, with obvious socio-economic benefits. A key question arises: are these benefits achieved at the expense of hard outcomes, such as patient survival? The answer is given by Figure 5: the median survival of the entire group of 202 patients was 5.5 years corresponding to an annual mortality rate of 12.6%. This rate is probably lower, but almost certainly not higher than that estimated in the period 2011-2013 for the Italian dialysis population, which was equal to 16.2 per 100 patient-years [28]. Figure 6 provides interesting information on the three groups of patients: it clearly shows the superiority of starting with 1HD/wk (G1) compared to starting with 2HD/wk or 3HD/wk, even if the intersection between the curves of G2 and G3 makes the difference among the three groups not statistically significant. The first obvious explanation is that the patients enrolled into the three groups may differ as far as phenotype and/or co-existence of underlying comorbid conditions are concerned. It is evident that this is the Achille's heel of any observational study design, in which an obvious selection bias (assignment of patients to different treatments) occurs. However, we think that the striking difference between G1+G2 and G3 in the late referral to our nephrology team, as shown in Table II (11.0% *vs*. 38.5%, P = 0.001), may be another important explanation. Therefore, we think that the synergistic interplay of the above factors, i.e., a different phenotype of the patients (for instance, as shown in Table II, there was a much larger percentage of women in G3 than in G1+G2: 61.5% *vs*. 35.6%, P = 0.003), co-existing underlying co-morbid conditions and a late referral, may constitute an ominous prognostic sign in G3.

In conclusion, our study seems to suggest that adequate educational, nutritional and pharmacological interventions in the pre-dialysis stage may allow a relatively good RKF and, therefore, the start of incremental dialysis in most of the incident patients. As far as the prescription of a low-protein diet is concerned, policy of our team is not to prescribe a very rigorous low-protein diet even when on once-a-week dialysis schedule, at variance with the advice given by some studies [29–32]. Only 4 patients enrolled into the study were prescribed keto-analogues in their pre-dialysis diet, which were continued when on dialysis, but only for some months and not for all the days of the week. All the other patients were prescribed a mild protein restriction when on dialysis, as shown by the PCRn values reported in Table III: at T3 PCRn in G1 on average was about 1 g/kg/day, while that in G2 was 1.13, almost comparable to 1.15 g/kg/day observed in G3. Furthermore, Tables IV and V show that PCRn values remained relatively constant over time. In conclusion, this study suggests that, in the presence of sufficiently elevated RKF (for instance, KRU in the range of 3-5 ml/min/1.73 m^2) a strict low-protein diet is useful but not essential, provided that the clinical status of the patient and his/her values of KRU, UO and PCRn are frequently monitored. This allows to considerably enlarge the number of patients eligible to start dialysis with one session a week, which in our study approached 60% (117/202 = 0.579) of all patients. This group of patients had a baseline GFR of 6.2 ±2.1 ml/min/1.73 m^2 and a baseline KRU of 4.5 ±1.6 ml/min/1.73 m^2. Furthermore, taking into account the patients who started with a twice-a-week dialysis schedule, the percentage of patients starting dialysis not on a thrice-a-week schedule exceeded 80% (163/202 = 0.807).

The analysis of Tables III, IV and V shows other interesting data, such as the relative constancy both of the duration of the session and of the dialysis dose, expressed by spKt/V and eKt/V. Therefore, the reduction of KRU was substantially compensated in G1 and G2 by increasing the frequency of the treatment. Here, it must be underlined that the prescription of the dialysis dose has been prevalently empirical worldwide, in the absence of shared criteria of dialysis adequacy of the incremental treatment, which have only recently been proposed [9, 22, 24]. Here, we have to acknowledge that we did not prescribe well-defined targets of the weekly dialysis dose to be

achieved by the patients, at least in the early years of the present study: thus, our prescription too was prevalently empirical, targeting urea clearance metrics of spKt/V ≥1.20, and increasing the frequency of treatment in the following situations: marked reduction in KRU (below 2-3 ml/min) and/or in UO (<500 ml/day); marked increase in inter-dialysis body weight, not controllable by increasing the dose of diuretics; need of ultrafiltration rate >13 ml/kg/h; symptoms or signs, such as nausea or malnutrition, that could not be controlled with medical therapy. More recently, we have suggested the criteria for the prescription of incremental dialysis on a quantitative basis associated with UKM [22, 24, 33, 34].

We have to acknowledge that our study has limitations, such as being a single-center retrospective observational study, but we have to underline its strengths, such as its long-term follow-up, and the availability of a large number of KRU and UO values measured in all patients with UO >200 ml/day. Despite increasing evidence derived from observational studies, such as ours, to support the use of incremental HD, randomized controlled trials (RCTs) are lacking and urgently needed. A multicenter feasibility RCT to assess the impact of incremental *vs.* conventional initiation of HD on RKF was recently conducted in the UK: serious adverse events were less frequent in the incremental arm; hospitalisation rate was higher in the control arm; in addition, median costs of the 12-month trial were higher in the standard care arm than in the incremental arm that benefited from reduced transport, session and adverse event costs [35].

At the present time no RCT testing incremental HD has yet been published. Of note, several ongoing RCTs are using thresholds of residual KRU to establish clinical effectiveness of less frequent HD in the form of once-a-week or twice-a-week HD *vs.* thrice-a-week HD [33, 34, 36, 37].

Conclusions

The optimal regimen for incident patients is not known. Incremental HD seems to be a valuable option, whereas it is plausible that the routine practice of fixed-dose 3HD/wk in incident patients with substantial RKF may be harmful, even contributing to an accelerated loss of RKF. Our long-term observational study suggests that incremental HD is a valuable option in incident patients and is possible in most cases (80.7%) for about 1-2 years, with obvious socio-economic benefits, and with survival rates comparable to that of the Italian dialysis population. If the potential benefits will be confirmed by RCTs, then incremental HD will become a new standard of care.

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