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Beyond 10 years of levodopa intestinal infusion experience: Analysis of mortality and its predictors

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ABSTRACT

Introduction: Although levodopa/carbidopa intestinal infusion (LCIG) proved a sustained efficacy on Parkinson's disease (PD) motor fluctuations, there is a lack of studies on mortality of LCIG patients. In this study, we aimed at analyzing mortality and its predictors in a cohort of 105 PD patients treated with LCIG for over 10 years.

Methods: The death rate, death causes, mortality predictors, and serious adverse events (SAEs) were analyzed. A Cox regression model was used to estimate the influence of several demographic and clinical factors on mortality, and a binary logistic regression to evaluate the association between SAEs number and mortality. Kaplan-Meier and Log-rank test was used for a survival comparison between patients with an early drop-out (within 3 years since LCIG start) and patients continuing LCIG.

Results: Ninety-eight advanced PD patients treated with LCIG were included. During follow-up, 34.7% of patients died at a mean age of 74.7 years, with a mean survival time of 4.6 years since LCIG start and 18 years since PD onset. The only predictor of mortality identified was the Mini Mental State Examination score at LCIG start (p:0.034). A total of 222 SAEs occurred in 87.9% of LCIG patients. The number of SAEs did not correlate with the mortality of LCIG patients (p:0.370). No survival difference exists between early drop-out patients and those continuing LCIG (p:0.341).

Conclusion: Our findings do not indicate an association between SAEs or LCIG treatment duration and mortality and highlight the importance of cognitive alterations as a mortality predictor of LCIG patients.

1. Introduction

The advanced phase of Parkinson's disease (PD) is characterized by therapy-related complications, erratic response to dopaminergic medications, and the onset of symptoms with poor levodopa response, which eventually result in shorter life expectancy [1].

Randomized controlled clinical trials demonstrated that device-aided therapies, encompassing continuous levodopa/carbidopa intestinal gel (LCIG) infusion, apomorphine infusion, and deep brain stimulation (DBS), can significantly reduce motor fluctuations in advanced PD [2–4]. Many other studies confirmed in real-life experience that LCIG is clinically effective in relieving not only PD cardinal symptoms, but also freezing of gait and non-motor symptoms [5,6]. As for DBS and apomorphine, LCIG demonstrated a sustained efficacy over the years, leading to significant improvement in activities of daily living (ADL) and quality of life (QoL) by means of a continuous levodopa delivery [7,8]. However, over time many concerns have risen regarding the complications experienced by patients during LCIG therapy, related both to the device and the drug [9,10]. Only a few studies reported the long-term outcome of LCIG therapy [7,8,11] and no studies aimed to analyze the mortality of PD patients under LCIG infusion therapy.

The primary aim of this study was to perform an analysis of mortality in 105 consecutive PD patients treated with LCIG for over 10 years. As secondary aims, we investigated predictors of mortality in the LCIG cohort and analyzed the serious adverse events (SAE) occurring during therapy, considering their potential correlation with the survival.

2. Methods

In this retrospective, longitudinal observational study we reviewed medical chart data and health information of all the 105 consecutive PD patients treated with LCIG at our institution between January 2005 and January 2019.

All data were extracted from the data system of the Movement Disorders Center of the University of Torino and, when necessary, by

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phone surveys to the patients or their families.

Inclusion criteria were: diagnosis of idiopathic PD [12], the presence of motor fluctuations, and the treatment with LCIG. The lack of follow-up data was an exclusion criterion from the study.

2.1. Outcome measures

Patients were divided into "alive" or "dead" at the time of follow-up (January 2019), and the mortality rate was calculated. The mean survival time was calculated as years of life between the date of percutaneous endoscopic trans-gastric jejunostomy (PEG-J) and the date of death. Additionally, follow-up was divided in short- (0–3 years), medium- (4–6 years), and long-term (≥7 years) and the mortality rate calculated for each follow-up interval.

Death causes were collected and divided into the following categories: inhalation pneumonia, cardio-circulatory/cerebrovascular disease, deterioration of general condition (death occurring in a very late stage of PD, in a patient unable to stand unassisted and chronically bedridden), sepsis, gastro-intestinal disorders, traumatic injuries, metabolic alterations, and unknown. Then, the causes of death were divided in *likely* or *unlikely* related to LCIG therapy.

All the available demographic and clinical variables at the time of LCIG start (baseline) were collected and analyzed: gender, age, disease duration, duration of motor fluctuations, stage of PD as per the Hoehn and Yahr score [13], Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II [14], MDS-UPDRS part III [14] in the 2 dopaminergic treatment conditions: "Off", after ≥ 12 h withdrawal from antiparkinsonian medication, and "On", about 45 min after the administration of a challenge levodopa dose consisting in 1.5x the usual effective dose taken in the morning before surgery, axial score (as per the sum of the following UPDRS items: speech; arising from a chair; posture; gait; and postural stability; range 0–20) in "Off" and "On" condition [15], Levodopa Equivalent Daily Dose (LEDD) [16], Mini Mental State Examination (MMSE) score [17], and Beck Depression Inventory (BDI) score [18]. Comorbidities were also collected and the Charlson Comorbidity Index (CCI) calculated for all patients [19]. A validated formula was used to convert UPDRS into MDS-UPDRS scores, when needed [20].

Moreover, all the therapy-related SAEs, defined per the FDA guidelines (https://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm), were analyzed and divided in: device-related (tube occlusion/tube break, accidental removal/dislocation of inner tube, duodenal decubitus ulcers, pump-related issues, gastro-intestinal disorders), peri-stomal-related (stoma leakage, skin infection, granulation tissue around stoma, buried bumper syndrome (BBS)), and levodopa infusion-related (acute/sub-acute polyneuropathy, psychosis). The correlation between the mortality and the number of SAEs reported by each patient was assessed.

The endoscopic procedures for PEG-J replacement were also analyzed, counted, and divided in ordinary replacement (i.e., PEG-J replacement for regular use) and extraordinary replacement when related to SAEs.

Finally, as exploratory outcome, we analyzed the mortality rate and causes of death of the subgroup of patients with an early drop-out from LCIG (i.e., removal of LCIG within 3 years since gastrostomy). Survival curves were compared between early drop-out and LCIG continuing patients.

2.2. Statistical analysis

Descriptive statistics (mean, standard deviation, and range) were used for continuous variables and frequency for categorical data. The standardized mortality ratio is the ratio of the observed and expected number of deaths and was calculated using data from the Italian Central Statistics Institute (ISTAT) (http://dati.istat.it/Index.aspx?DataSetCode=DCIS_MORTALITA1). A Cox regression model was used to estimate the influence of the following factors on the mortality of LCIG patients: age, disease duration, MDS-UPDRS part III in "Off" and "On" condition, axial score in "Off" and "On" condition, MMSE, Hoehn and Yahr, and CCI. Variables having clinical relevance or p-value ≤ 0.1 at univariate analysis were retained in the final model. MMSE was first used as a continuous variable in the statistical model. Then the analysis was repeated using MMSE as dichotomous variable, using a cut-off of 26 to distinguish preserved cognition (MMSE score ≥ 26) from cognitive impairment (MMSE score < 26) [21].

A binary logistic regression analysis was performed to evaluate the association between the number of SAEs of each LCIG patient and the mortality (dependent variable).

The Mann-Whitney *U* test (continuous variables) or Fisher exact test (categorical variables) were used to compare the following demographic and clinical data between the two groups of LCIG patients (continuing vs. early drop-out): sex, age, disease duration, duration of motor fluctuations, total LEDD, dopamine-agonist (DA) LEDD, levodopa LEDD, MDS-UPDRS-II, MDS-UPDRS-III, axial score, Hoehn and Yahr score, BDI score, MMSE score, CCI score. Kaplan-Meier survival analysis and log-rank test were used to compare the survival of the two groups of LCIG patients (continuing vs. early drop-out).

All p-values reported are two-tailed, and a $p < 0.05$ was considered statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS 22 for Mac, Chicago, IL). This analysis was performed for the purpose of internal quality control. Data entered into the database were analyzed anonymously, and the local ethical committee approved the study.

3. Results

Seven patients had incomplete or missing data and were excluded from the study. Complete data were available for 98 LCIG patients (Table 1): 100% (n = 98/98) reached the short-term, 76.5% (n = 75/98) the medium-term, and 38.8% (n = 38/98) the long-term follow-up, for a mean cumulative follow-up period of 490 patient-years. The mean age at LCIG start was 67.9 ± 7.3 years (range 44–80), and the mean disease duration 13 ± 4.3 years (range 5–28).

Table 1
Demographic and clinical data of patients before LCIG start.

Data of the 98 LCIG patients enrolled	
Sex (males/females)	63/35
Age (years)	67.9 ± 7.3 (44–80)
Disease duration (years)	13 ± 4.3 (5–28)
Motor fluctuations duration (years)	5.2 ± 2.9 (1–18)
Total LEDD (mg)	1148 ± 447.4 (400–2480)
DA-LEDD (mg)	172.3 ± 186.8 (0–930)
Levodopa-LEDD (mg)	1030 ± 386.1 (125–2400)
Patients using DA (yes/no)	33/65
MDS-UPDRS-II	17.8 ± 7.6 (4–40)
MDS-UPDRS-III "OFF"	57.7 ± 12.7 (19–82)
MDS-UPDRS-III "ON"	31.2 ± 12.4 (7–56)
Axial score "OFF"	11.6 ± 3.8 (2–17)
Axial score "ON"	6.6 ± 3.4 (0–15)
Hoehn and Yahr	2.6 ± 0.7 (1–4)
Beck Depression Inventory	15.4 ± 7.8 (1–33)
MMSE	26.3 ± 3.3 (15–30)
Follow-up duration since LCIG start (years)	5.3 ± 2.7 (0–12)

Values are expressed as mean ± standard deviation (range).
LCIG = levodopa/carbidopa intestinal gel.
LEDD = levodopa equivalent daily dose.
DA = dopamine agonist.
MDS-UPDRS = Movement Disorders Society - Unified Parkinson's Disease Rating Scale.
MMSE = Mini Mental State Examination.

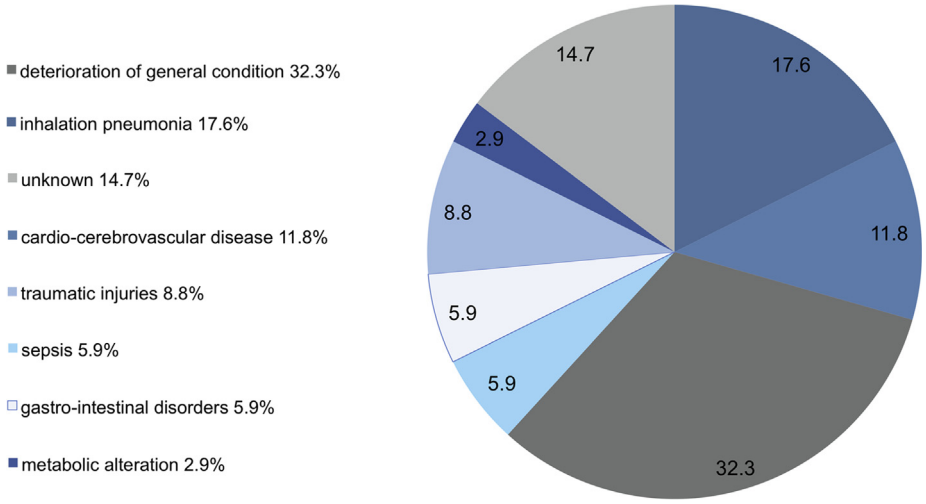

Fig. 1. Causes of death in LCIG patients.

3.1. Analysis of mortality

During follow-up, 34.7% of LCIG patients died (n = 34/98). The annualized mortality rate was 4.4% in the short-term follow-up, 8.1% in the medium-term, and 5.5% in the long-term. The standardized mortality ratio was 3.5.

Among the subgroup of patients who died, the mean survival time since LCIG start was 4.6 ± 2.6 years (range 0.3–11), the mean PD duration at death was 18 ± 5.2 years (range 8–33), and the mean age at death was 74.7 ± 7.6 years (range 52–85). The number of LCIG patients and deaths per year of follow-up are reported in Supplementary Fig. 1.

3.2. Causes of death

The causes of death were deterioration of general condition in 32.3% of patients (n = 11/34), inhalation pneumonia in 17.6% (n = 6/34), unknown in 14.7% (n = 5/34), cardio-cerebrovascular disease in 11.8% (n = 4/34), traumatic injuries in 8.8% (n = 3/34), sepsis in 5.9% (n = 2/34), gastro-intestinal disorders in 5.9% (n = 2/34), and metabolic alteration in 2.9% (n = 1/34) (Fig. 1).

All the traumatic injuries were caused by falls, associated with post-traumatic subdural hematoma (n = 2) and femur fracture (n = 1); sepsis was related to spondylodiscitis (n = 1) and urinary tract infection (n = 1); gastro-intestinal disorders were related to intestinal occlusion (n = 1) and hepatic failure (n = 1); the metabolic alteration was caused by severe hypoglycemia.

One cause of death pertaining to the gastro-intestinal disorders was considered *likely* related to the LCIG infusion therapy: the patient died for intestinal occlusion three months after LCIG start. All other causes of death were classified as *unlikely* related to LCIG therapy.

The causes of death divided into short-, medium-, and long-term follow-up are reported in Table 2.

3.3. Predictors of mortality

According to the Cox regression analysis, we found that the MMSE score predicts mortality in LCIG patients, with lower MMSE score at LCIG start as a risk factor for mortality (p: 0.034; Hazard ratio: 0.873; 95% CI 0.771–0.990). We found a 2.8 higher risk of mortality in patients with a MMSE score < 26 at LCIG start (p: 0.026; Hazard ratio: 2.841; 95% CI 1.135–7.108).

Age, disease duration, MDS-UPDRS part III in "Off" and "On" condition, axial score in "Off" and "On" condition, Hoehn and Yahr, and CCI did not show a significant association with mortality (Supplementary Table 1).

Table 2
Causes of death at different follow-up periods.

	Short-term (0–3 years)	Medium-term (4–6 years)	Long-term (≥7 years)
Inhalation pneumonia	3	2	1
CCD/CVD	0	4	0
Deterioration of general condition	2	4	5
Sepsis	2	0	0
GI disorders	1	1	0
Traumatic injuries	2	1	0
Metabolic alterations	1	0	0
Unknown	2	2	1

CCD/CVD = cardiocirculatory disease/cerebrovascular disease.
GI = gastrointestinal.

3.4. Analysis of serious adverse events (SAEs)

Data on SAEs were available for 91/98 patients because 7 patients had not been regularly followed-up at our Center. During a cumulative period of 455 patient-years (5 years for 91 patients), we found 222 SAEs occurring in 87.9% of patients (n = 80/91). SAEs were distributed as follows: 70.3% device-related (n = 156/222), 24.3% peri-stomal-related (n = 54/222), and 5.4% levodopa infusion-related (n = 12/222). The most common device-related SAE was the occlusion or break of the PEG-J jejunal-tube, the most common peri-stomal-related SAE was granulation tissue around the stoma, and the most common levodopa infusion-related SAE was polyneuropathy (Supplementary Fig. 2).

The number of SAEs did not correlate with the mortality of LCIG patients (Odds ratio: 0.904; p: 0.370).

3.5. Specific analysis on iatrogenic neuropathy

A total of 11% of patients (n = 10/91) developed an acute/subacute polyneuropathy. The mean latency of neuropathy onset from LCIG start was 2.2 ± 1.3 years (range 0.5–4). Sixty percent of patients (n = 6/10) received an electrophysiological diagnosis of demyelinating polyneuropathy with conduction blocks, while the remaining showed the new onset or a marked worsening of an axonal polyneuropathy. All patients performed a nerve conduction study early before starting LCIG, and all of them showed either normal findings or mild subclinical alterations.

The mean disease duration of patients who developed

polyneuropathy was 18 ± 5 years (range 9–26). Fifty percent of these patients (n = 5/10) died 2.4 ± 2.2 years (range 1–6) after the polyneuropathy onset. The mean age at death was 75 ± 10.9 years (range 63–87). No patients died because of polyneuropathy.

3.6. LCIG drop-out, gastric infusion, and PEG-J replacements

A total of 22% of patients (n = 20/91) dropped-out LCIG after a mean therapy duration of 3 ± 2.6 years (range 0–8). The drop-out reasons were: no clinical benefit in 10% of patients (n = 2/20), abdominal pain in 10% (n = 2/20), PEG-J displacement/surgical abdominal complications in 10% (n = 2/20), poor compliance in the management of LCIG device in 5% (n = 1/20), late stage PD in 20% (n = 4/20), and neuropathy in 45% (n = 9/20).

An additional 8.8% of patients (n = 8/91) was converted to levodopa/carbidopa gel gastric infusion (with the removal of the inner tube) because of repeated accidental tube occlusion or tube connection break-down.

The number of ordinary PEG-J replacements was 168. A total of 69.2% of patients (n = 63/91) needed extraordinary PEG-J replacements, for a total of 130 additional endoscopic procedures. This data resulted in a mean of 3.3 procedures per patient (1.9 ordinary and 1.4 extraordinary PEG-J replacements per patient).

3.7. Analysis of mortality in early drop-out patients

15.3% of patients (n = 15/98) dropped-out LCIG after a mean follow-up time of 1 ± 1.2 years (range 0–3). Drop-out causes were neuropathy (n = 6), psychosis (n = 1), tube dislocation (n = 1), no clinical benefit (n = 4), pain (n = 1), and general condition deterioration (n = 2). Clinical/demographic features did not show a significant difference between the group of early drop-out and the other LCIG patients (Supplementary Table 2). Patients with an early drop-out showed a mortality rate of 46.7% (n = 7/15), which did not differ significantly from the mortality rate of patients continuing LCIG (p: 0.378). Among the subgroup of patients who died, the mean survival time since LCIG start was 4.8 ± 2.3 years (range 3–9), the mean PD duration at death was 17.4 ± 1.6 years (range 15–20), the mean age at death was 74.3 ± 7.2 years (range 61–82), and the mean survival time since LCIG drop-out was 2.9 ± 2.9 (range 0–8).

No significant difference in the survival curves was found between the group of patients treated with LCIG in the long-term and the group with an early drop-out (log rank test p: 0.341) (Fig. 2).

4. Discussion

This study presents an extensive analysis of mortality and its predictors in a large cohort of PD patients treated with LCIG. In a follow-up period of over 10 years, 34.7% of patients died at a mean age of 74.7 years, 4.6 years after LCIG start, and after 18 years of disease duration. The only predictor of mortality was the MMSE score. Moreover, we observed a high number of SAEs (n = 216) related to LCIG therapy, mostly due to device issues. However, we could not find a correlation between SAEs and causes or probability of death. Finally, the subgroup of patients with an early LCIG withdrawal showed a similar rate of mortality than patients continuing LCIG for a more extended period.

To our knowledge, this is the first study assessing mortality and its predictors in PD patients treated with LCIG. Several studies suggested a reduction of mortality in PD patients following the introduction of levodopa [22,23]; however, a significant change in the natural history of the disease has never been demonstrated, and the mortality ratio in PD is still higher compared to the general population, ranging from 1.1 to 3.8 [24]. The more recent advent of device-aided therapies has changed the perspective of advanced PD, providing additional years of acceptable management of cardinal symptoms and motor complications and improving patients' ADL and QoL [3,7,8]. In the context of mixed literature results, recent studies suggested that patients treated with DBS might have a slightly longer survival when compared with patients treated with standard medical management [25,26], and it has been hypothesized that this survival advantage might be related to the sustained improvement of motor function rather than a disease-modifying effect [25]. Even though PD patients treated with LCIG show a motor improvement that is comparable to the one showed by patients treated with DBS [27], it has been postulated that the repeated endoscopic procedures and the interaction between LCIG and intestinal absorption, with the consequent weight loss and polyneuropathy, might worsen patients' condition and eventually impact the survival [28,29].

No negative impact of LCIG treatment duration or SAEs on survival emerged in our large cohort of patients followed-up for over 10 years. In fact, LCIG patients died after a mean PD duration of 18 years, which reflects current evidence on the survival of PD patients treated with standard medical management [24]. Studies assessing mortality from cohorts of PD patients undergoing DBS surgery, which typically include well-selected patients with a good prognosis (i.e., absence of cognitive impairment and severe axial symptoms), reported a mean disease duration ranging from 21 to 23 years and a mean age at death ranging from 65 to 76 years [15,25,26]. These data reflect the mean disease duration and age at death observed in our cohort. Moreover, the mortality rate observed in the group of patients with early discontinuation of LCIG was similar to the one of the group continuing LCIG. Altogether, these findings suggest that prolonged LCIG therapy does not have a relevant impact on the survival of PD patients.

Investigating the potential predictors of mortality among numerous clinical and demographic features, we observed that a lower MMSE score before starting LCIG negatively influenced survival. In particular, we found that a MMSE cut-off of 26 is significantly associated with mortality, with patients scoring < 26 having a 2.8 higher risk of death. This finding highlights the predictive value of cognitive alterations not only on patients' independence and QoL but also on mortality, confirming data from previous studies assessing mortality predictors in the natural history of PD [30,31].

Regarding SAEs, the rate of device-related issues that we observed (222 SAEs occurring in 87.9% of patients) is significantly higher than reported in clinical trials on LCIG, where their frequency ranged from 14 to 53% [2,7]. This observation is not surprising considering the long-term follow-up of the present study and the differences between real-life studies and clinical trials. On the other hand, the prevalence of acute/subacute polyneuropathy we have found (11%) is similar to the one previously reported in the literature [29,32] and not higher, as expected in a long-term evaluation. This finding might be related to the typical early occurrence of the LCIG-associated acute/subacute polyneuropathy, potentially strengthening the dysimmune/inflammatory hypothesis of this adverse event, compared to the "chronic" deficiency hypothesis [29]. Moreover, we observed a high rate of demyelinating polyneuropathy (60% of recorded polyneuropathies), which can appear higher than data reported in the literature [32]. This finding may be explained by the fact that we reported only severe, acute or subacute forms of polyneuropathy, requiring hospital admission and therapy withdrawal. Chronic forms of polyneuropathy, more typically related to axonal polyneuropathy, may be therefore under-reported in our cohort. Finally, only a very small percentage of the observed SAEs could be associated with death, and we did not find any correlation between the number of SAEs and the survival of patients.

Some limitations temper the strength of our results. First, the retrospective study design might have underestimated the number of SAEs recorded, and other relevant LCIG-related complications, such as the weight loss, have not been consistently recorded. Second, in 14% of dead patients, we could not retrieve the cause of death, due to missing information. Third, the comparison of the mortality rate in our cohort is limited to a small group of early LCIG drop-out patients and literature data since we could not rely on a matched control group.

Taking into account these shortcomings, our findings do not

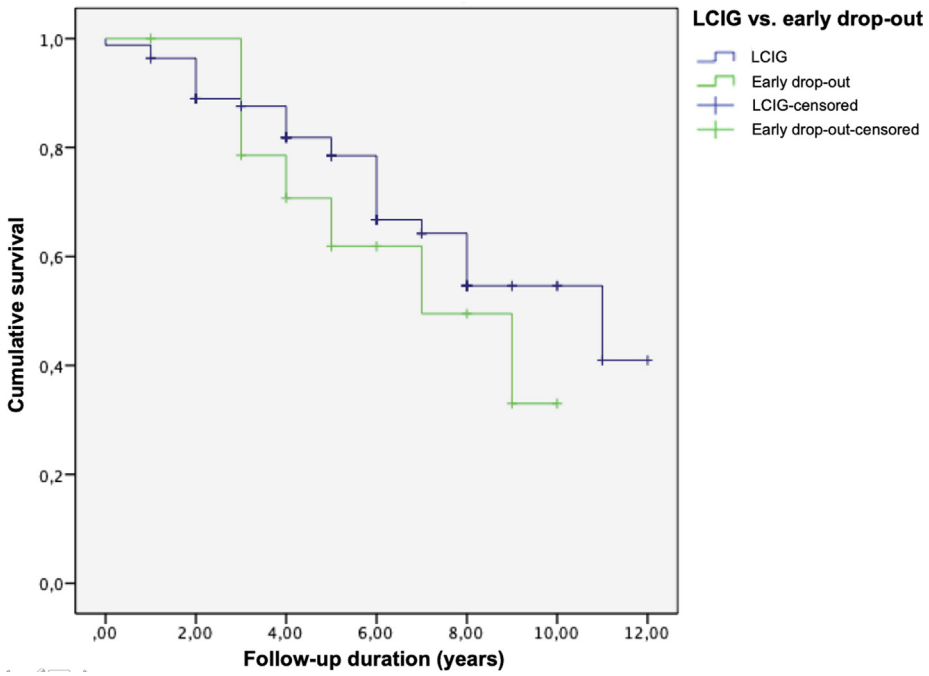

Fig. 2. Survival curves.

indicate an association between LCIG and mortality and highlight the high rate of SAEs related to the therapy and its device. Considering the high efficacy of LCIG in advanced PD, our results emphasize the importance of a careful selection of patients, and advise the frequent monitoring of treated patients, paying particular attention to device-related issues and clinical or neurophysiological signs of polyneuropathy. In particular, our data suggest a cautious use of LCIG in patients with cognitive alterations, given the impact of cognitive deficits on device management and, eventually, on survival.

Author roles

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique.

Carlo Alberto Artusi: 1B, 1C, 2A, 2B, 3A
Roberta Balestrino: 1C, 2C, 3B
Gabriele Imbalzano: 1C, 3B
Sara Bortolani: 1C, 2C, 3B
Elisa Montanaro: 1C, 3B
Sara Tuttobene; 1C, 3B
Margherita Fabbri: 1C, 2C, 3B
Maurizio Zibetti: 1B, 1C, 2C, 3B
Leonardo Lopiano: 1A, 1B, 2C, 3B

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Declaration of competing interest

All authors report no disclosures and no conflict of interests concerning the research related to the manuscript.

Appendix A. Supplementary data

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