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Can Early Introduction of Palliative Care Limit Intensive Care, Emergency and Hospital Admissions in Patients with Severe Chronic Obstructive Pulmonary Disease? A Pilot Randomized Study

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Keywords

Chronic obstructive pulmonary disease · Palliative care · Long-term oxygen therapy · Home noninvasive ventilation · Symptom control

Abstract

Background: Despite their poor prognosis, patients with severe chronic obstructive pulmonary disease (COPD) have little access to palliative care and tend to have a high rate of hospital and intensive care unit (ICU) admissions during their last year of life. ***Objectives:*** To determine the feasibility of a home palliative care intervention during 1 year versus usual care, and the possible impact of this intervention on emergency, hospital and ICU admissions, survival, mood, and health-related quality of life (HRQL). ***Methods:*** Prospective controlled study of patients with severe COPD (GOLD stage III or IV) and long-term oxygen therapy and/or home noninvasive ventilation and/or one or more hospital admissions in the previous year for acute exacerbation, randomized to usual care versus usual care with add-on monthly intervention by palliative care specialists at home for 12 months. ***Results:*** Of 315 patients screened, 49 (15.5%) were randomized (26 to early palliative care; 23 to the control group); aged (mean ± SD) 71 ± 8 years; FEV_1 was 37 ± 14% predicted; 88% with a COPD assessment test score >10; 69% on long-term oxygen therapy or home noninvasive ventilation. The patients accepted the intervention and completed the assessment scales. After 1 year, there was no difference between groups in symptoms, HRQL and mood, and there was a nonsignificant trend for higher admission rates to hospital and emergency wards in the intervention group. ***Conclusion:*** Although this pilot study was underpowered to formally ex-

This trial was registered at clinicaltrials.gov (NCT02223780).

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clude a benefit from palliative care in severe COPD, it raises several questions as to patient selection, reluctance to palliative care in this group, and modalities of future trials.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disorder leading to chronic respiratory failure, respiratory distress, and recurrent hospitalizations for acute exacerbations (AECOPD). Mortality rates of 30–50% have been reported within 2 years following hospital admission for acute exacerbations [1–4]. An estimated 30% of COPD patients hospitalized for the first time are re-admitted within 3 months. While medical treatment may partially relieve symptoms and noninvasive ventilation (NIV) and oxygen therapy may prolong life [5], for patients with severe COPD, both quality of life and survival are poor [6–8]. In spite of this, COPD patients are much less likely to receive palliative care than patients with lung cancer [9–14]. In fact, COPD patients have limited access to specialists in palliative care [15, 16] and very few palliative care intervention studies are available for this population [17, 18].

The "SUPPORT" study demonstrated that COPD patients, when compared to patients with lung cancer, were much more likely to die in the intensive care unit (ICU), on mechanical ventilation and with dyspnea [19, 20]. These differences occurred although most patients with COPD preferred treatment focused on comfort rather than on prolonging life. In fact, "SUPPORT" found that patients with lung cancer and COPD were equally likely to prefer *not* being intubated, and *not* receiving cardiopulmonary resuscitation (CPR), yet patients with COPD were much more likely to receive these therapies.

Because of these observations, advance care planning (ACP) should be especially appropriate among patients with COPD: their unpredictable trajectory of illness and exacerbations may make these patients suddenly critically ill. However, only a minority of patients with moderate-to-severe COPD have discussed treatment preferences and end-of-life care issues with their physicians [21, 22]. In fact, most COPD patients believe that their physicians do not know their preferences for end-of-life care. Severe COPD also represents a substantial and prolonged burden in terms of care, with often a poor control of symptoms and emotional disorders.

The aim of this pilot prospective randomized study was to evaluate the feasibility and possible impact of an early palliative care intervention at home in severe and very severe COPD patients over a 1-year period. Because admissions to emergency wards, hospitalizations and admissions to ICUs are distressing experiences for these patients, and represent a substantial financial burden, we defined these items as major endpoints of our intervention. We added a detailed evaluation of symptoms, health-related quality of life (HRQL), and mood disturbances as secondary endpoints. Our hypotheses were that patients would accept and benefit from a palliative care intervention and that, through improved understanding of their disease and symptom management, and promotion of ACP, requirements for in-hospital acute care would decrease.

Patients and Methods

Patients were recruited among subjects followed by Geneva University Hospitals on long-term oxygen therapy (LTOT) and/or home NIV, and subjects hospitalized for AECOPD in our general internal medicine and geriatric wards.

Details of the study protocol have previously been published [23]. Briefly, inclusion criteria were: COPD defined according to GOLD (Global Initiative for Obstructive Lung Diseases; www.goldcopd.org) criteria (FEV_1/FVC <70%) stage III or IV (FEV_1 <50% predicted) and LTOT and/or home NIV and/or one or more hospital admissions in the previous year for an acute exacerbation. Exclusion criteria were: moderate or severe cognitive impairment (Mini Mental State Examination [MMSE] score <23) and cancer.

After providing written informed consent and filling in baseline measurements, patients were randomly assigned to the early palliative care group (EPC) or the standard care group (SC) in a 1:1 ratio without stratification and with randomized block sizes ranging from 4 to 6, using sealed envelopes prepared with a computer program by F.R.H., a co-investigator not involved in the inclusion of the patients.

Intervention

Patients assigned to the EPC group met our community ambulatory palliative care team as soon as possible after inclusion and monthly thereafter for 12 months. Home visits by nurses from the palliative care consultation lasted approximately 90 min and focused on:

- *Symptom assessment and management* using the Edmonton Symptom Assessment Scale (ESAS) [22, 23]. If intensity of pain, dyspnea, mood, anxiety, and appetite were >4/10 and the patient agreed, a consultation with a palliative care physician (or other specialist) was suggested
- *Nutrition* (Mini Nutritional Assessment Scale) [24]
- *Understanding of illness and coping*: information about COPD was provided through patient education, and use of brochures on activities of daily living [25]; management of acute and chronic dyspnea were discussed as well as use of morphine
- *Anticipation, decision-making*: completion of ACP was systematically discussed and encouraged

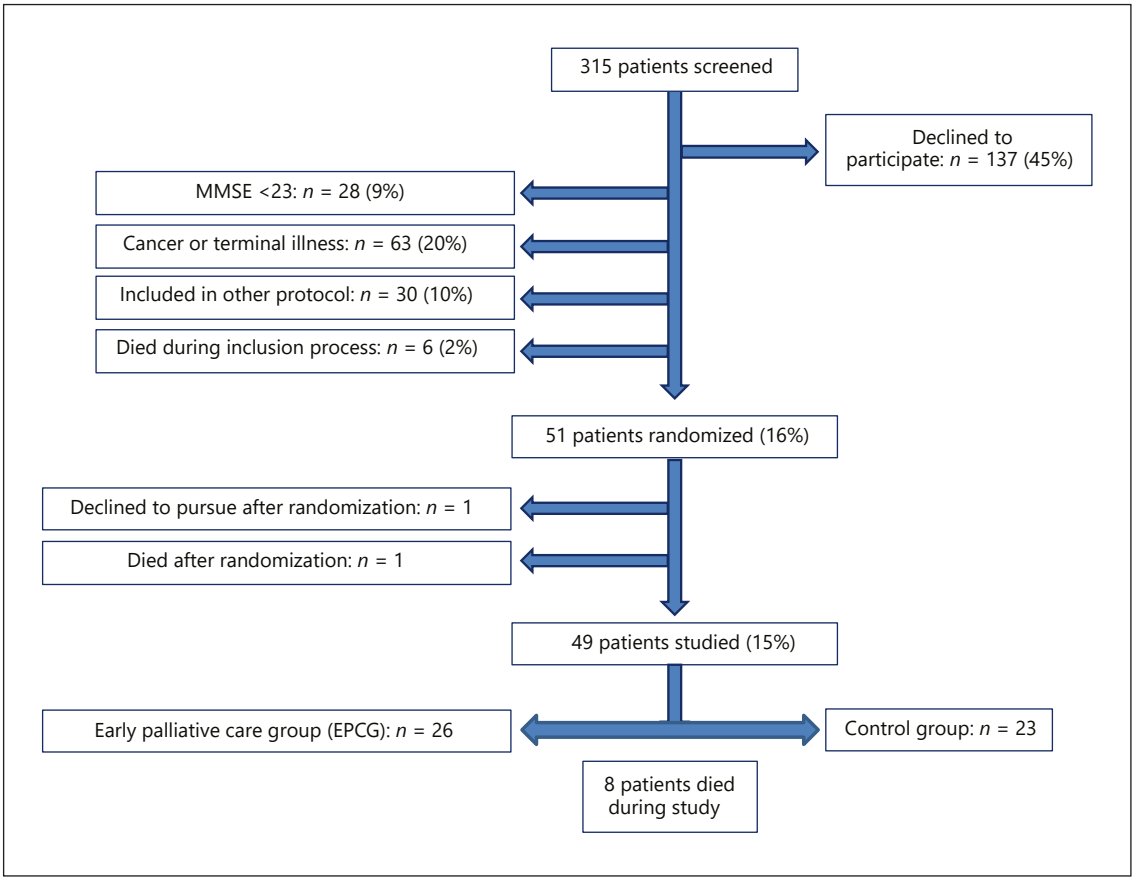

Fig. 1. Flowchart of the study up to randomization and patients deceased during the study.

- *Support of relatives* was provided by meeting caregivers, and support interviews
- *Social-spiritual needs* were identified, and, when appropriate, support was provided
- Coordination between different health providers
- Alternative approaches such as relaxation, reflexology, massages

All cases were discussed with a physician specialized in palliative care, whom the patient could consult whenever appropriate. The palliative care team could be reached between visits if requested.

Control Group

Patients randomized to the SC group had no contact with the palliative care team. Both groups received standard care throughout the study period. For all patients under LTOT and/or home NIV, specialized nurses provided regular home visits to check on all aspects related to respiratory support. Treatments prescribed by a primary care physician or pulmonologist (chest therapy, physiotherapy, other aspects of home care) were not modified. Health care workers following the control group were not informed of the content of the "palliative care" intervention. Because the palliative care team was distinct from those providing standard care, the risk of "contamination" of the control group by the early palliative care intervention was minimal.

For both groups, a research nurse (independent from the palliative care team) performed a standardized evaluation including:

- At inclusion: basic sociodemographic data, MMSE, spirometry, use of oxygen or NIV, history of recent exacerbations (<3 months), prior admissions to the emergency ward, hospital, ICU, medication, network of health care workers and informal support (family), ACP
- Every month: data related to primary outcomes (hospital, emergency ward and ICU admissions) recorded through hospital files, contact with the patient and his/her GP
- Every 3 months: data related to primary outcomes; COPD assessment test (CAT) [26]; Hospital Anxiety and Depression scale (HAD) [27]; SF-36 HRQL scale [28]

This agenda was followed for 12 months. A final questionnaire (focused on satisfaction with and acceptability of the intervention) was submitted to all patients 6 months after the end of the intervention.

All data were anonymized and recorded on Secutrial software, and, at the end of data collection, transferred to our statistician (F.R.H.) for analysis. The trial was registered at clinicaltrials.gov (NCT02223780).

Table 1. Data at inclusion

	Early palliative care Group (n = 26)	Control group (n = 23)	All patients (n = 49)	p value
Age, years	70.8±8.4	71.3±8.1	71.1±8.2	0.820
Female	12 (46.2)	14 (60.9)	26 (53.1)	0.393
Pulmonary function tests				
FEV_1, L	0.86±0.41	0.87±0.3	0.87±0.37	0.924
FEV_1, % predicted	34.5±11.7	39.5±15.9	36.8±13.9	0.213
FVC, L	1.79±0.68	1.65±0.8	1.73±0.71	0.511
FVC, % predicted	60.9±18.3	58.8±21.9	60±19.7	0.716
BMI, kg/m^2	24.6±6.1	24.9±8.3	24.8±7.2	0.449
Respiratory support				
LTOT and/or NIV	19 (73.1)	15 (65.2)	34 (69.4)	0.757
Home NIV	10 (38.5)	5 (21.7)	15 (30.6)	0.233
Home oxygen therapy	17 (65.4)	12 (52.2)	29 (59.2)	0.394
Hospitalized within the year prior to study	18 (69.2)	18 (78.3)	36 (73.5)	0.532
Past history of smoking	24 (92.3)	20 (87.0)	44 (89.8)	0.655
Active smoking	8 (30.8)	8 (34.8)	16 (32.7)	0.757
Passive exposure	20 (76.9)	15 (65.2)	35 (71.4)	0.528
Care by home nurses	8 (30.8)	7 (30.4)	15 (30.6)	0.613
Home visits by specialized nurse	8 (30.8)	8 (34.7)	16 (32.6)	0.764
Home physiotherapy	9 (34.6)	9 (39.1)	18 (36.7)	0.377
Other home care	2 (7.7)	4 (17.4)	6 (12.2)	0.276

Values are presented as mean ± SD or n (%). FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; BMI, body mass index; LTOT, long-term oxygen therapy; NIV, noninvasive ventilation; SD, standard deviation.

Statistical Analysis

Group comparisons were performed using the Mann-Whitney U test, Student's t test, the Fisher exact or χ^2 tests, as appropriate. Survival data and a composite variable (i.e., any admission to hospital for cardiac or respiratory causes or death) were compared between groups using Kaplan-Meier curves and log-rank tests. Scores which were filled in repeatedly (HAD, SF-36 scores and subscores) were analyzed using mixed linear regression with visit, group and visit × group interaction as predictors, while taking into account the exact date of the visit. Number of hospitalizations and admissions were analyzed using incidence rate ratios computed with Stata's "iri" command. The Benjamini and Hochberg correction for multiple testing was applied for Table 3.

All statistical analyses were performed using the Stata software, version 14.2.

Results

Among 315 patients screened over an 18-month period, 137 (43%) refused to participate; 28 patients (9%) did not fulfill MMSE inclusion criteria (MMSE score >23); 63 (20%) had either cancer or another comorbidity limiting their short-term prognosis; 11 (3.4%) were included in another protocol; and 6 died rapidly during the inclusion process (Fig. 1, flowchart). None of the patients from the geriatric ward (n = 45) fulfilled MMSE inclusion criteria. Fifty-one patients were finally included. Of these, 1 (EPC group) died before the first home visit by the palliative care nurse. Another patient declined pursuing the study just after randomization when he learned that he was allocated to the control group. Thus, 49 patients were analyzed (26 in the EPC group and 23 in the SC group); 36 (73%) had been hospitalized during the previous year; all were GOLD stage III or IV, group D. Eight (16%) patients had died at the end of the study (1 in the ICU, 2 at home, and 5 in hospital wards).

Sociodemographic and functional data at inclusion are summarized in Tables 1 and 2, and in the online supplement (see www.karger.com/doi/10.1159/000495312 for all online suppl. material). For all items provided, the randomization process performed well, and there were no significant differences between groups for sociodemographic, anthropometric, functional and subjective variables. This was also the case for hospital, emergency ward and ICU admissions during the year prior to inclusion

Table 2. Data at inclusion regarding cognition (MMSE), symptoms (CAT), mood disturbances (HAD), and health-related quality of life (SF-36)

	Early palliative care group (n = 26)	Control group (n = 23)	All patients (n = 49)	p value
MMSE	29.8±1.6	28.1±0.5	29.0±0.9	0.127
COPD assessment test (CAT)	18.3±7.6	20.5±6.9	19.4±7.3	0.296
CAT >10	21 (80.8)	22 (95.7)	43 (87.8)	0.194
HAD anxiety scale (HAD A)	6.9±3.8	5.6±3.5		0.221
HAD A: analysis by category				0.154
Patients with HAD A <8	13 (50.0)	10 (43.5)	23 (46.9)	
Patients with HAD A 8–10	4 (15.4)	9 (39.1)	13 (26.5)	
Patients with HAD A >10	9 (34.6)	4 (17.4)	13 (26.5)	
HAD depression scale (HAD D)	8.3±4.5	6.9 (3.5)		0.234
HAD D: analysis by category				0.734
Patients with HAD D <8	17 (65.4)	18 (78.3)	35 (71.4)	
Patients with HAD D 8–10	4 (15.4)	2 (8.7)	6 (12.2)	
Patients with HAD D >10	5 (19.2)	3 (13.0)	8 (16.3)	
Short-Form 36 HRQL subscores (SF-36)				
Vitality	36.2±19.9	35.2±20.0	35.7±37.6	0.862
Mental health	60.9±27.7	60.0±24.1	60.5±25.8	0.904
General health	31.5±22.4	38.1±18.7	34.6±20.8	0.272
Physical functioning	29.0±19.1	27.8±22.1	28.5±20.4	0.839
Role physical	49.0±45.0	46.7±45.4	48.0±44.7	0.859
Role emotional	50.0±46.4	51.5±43.3	50.7±44.6	0.907
Bodily pain	48.2±24.6	42.9±23.2	45.7±23.8	0.443
Social functioning	58.7±32.7	50.5±31.4	54.8±32.0	0.376
Health transition	60.6±23.6	63.0±23.7	61.7±23.4	0.206

Values are presented as mean ± SD or n (%). MMSE, Mini Mental State Examination; HAD, Hospital Anxiety and Depression score for anxiety (HAD A) and Depression (HAD D): values between 8 and 10 considered borderline; values above are abnormal; SF-36: short-form 36.

(Table 3). Pulmonary function tests confirm the severe/very severe obstructive syndrome related to COPD (GOLD stage III or IV, group D criteria). Approximately 70% of all patients were either on LTOT, home NIV, or both; 73.5% had been hospitalized within the year prior to inclusion in our study for AECOPD. One third of patients were on antidepressant or anxiolytic medication, and 16% were on opiates.

Admissions to Emergency Wards, ICU, and Hospitalizations

As shown in Table 3, patients in the EPC group were hospitalized for respiratory failure (IRR 1.87, 95% CI 1.04–3.48, p = 0.026) and admitted to the emergency ward (IRR 2.05, 95% CI 1.11–3.94, p = 0.014) twice as often during follow-up than the control group. However, after the Benjamini and Hochberg correction for multiple testing, none of these differences was significant. Furthermore, when the same data are expressed as number of events by patient, median values are identical in both groups (hospitalization: median [IQR]: 0.0 [1; 2] vs. 1.5 [1; 4], p = 0.219; admissions to emergency wards: 1–0 [0; 3] vs. 1.0 [0; 4], p = 0.484). Figure 2 shows a Kaplan-Meier curve for a composite variable (admission to hospital or death) for both groups. The log-rank test did not show any significant difference between groups.

The use of antibiotics (for exacerbations not leading to hospital admission) did not differ between groups during the observation period (p = 0.819).

Health-Related Quality of Life (SF-36)

Average values at inclusion are provided in Table 2; online supplementary Figures 3S–10S show longitudinal follow-up of all subscores of the SF-36. Each figure shows expected values for a normal Swiss population matched for age and gender [29]. None of the items differed significantly between groups at inclusion or during follow-up. The most severely affected scores at inclusion were

Table 3. Admissions to hospital, intensive care unit (ICU) and emergency ward, the year preceding study, and during follow-up period

	Early palliative care group (n = 26)	Control group (n = 23)	All patients (n = 49)	Incidence rate ratio	95% CI	p value
Hospital admissions for respiratory failure						
Year before inclusion	24	18	42	1.18	0.61–2.31	0.603
During study period	38	18	56	1.87	1.04–3.48	0.026
Other hospitalizations						
Year before inclusion	8	6	14	1.18	0.36–4.12	0.772
During study period	8	7	15	1.01	0.32–3.28	0.988
Admissions to emergency ward						
Year before inclusion	33	23	56	1.27	0.72–2.26	0.384
During study period	37	16	53	2.05	1.11–3.94	0.014
Admissions to ICU for respiratory failure						
Year before inclusion	7	7	14	0.88	0.26–2.96	0.822
During study period	5	1	6	4.42	0.49–20.92	0.163

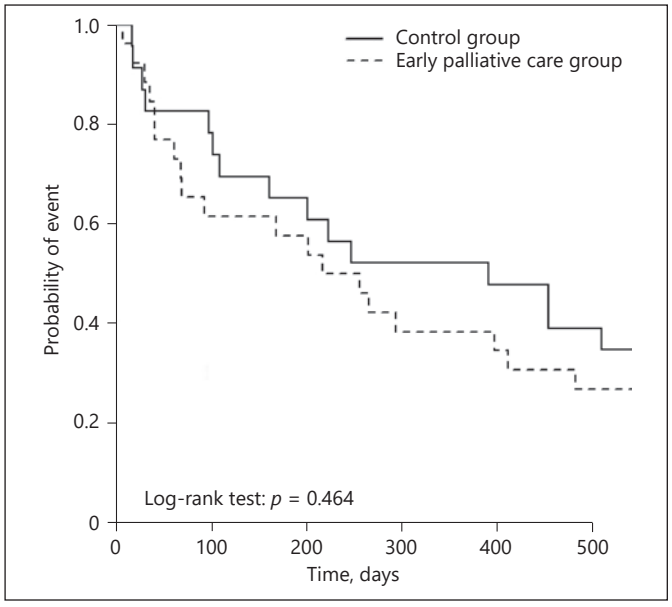

Fig. 2. Kaplan-Meier graph for composite endpoint (hospitalization for cardiopulmonary exacerbation or death) for the control group and intervention group and result of the log-rank test.

"vitality," "general health," "physical functioning," "role physical," and "bodily pain." After a slight insignificant improvement during the first 2 home visits, score values remained stable during follow-up.

Mood Disturbances: Hospital Anxiety and Depression Scale Scores (HAD A and HAD D)

Scores for HAD are considered normal if <8, borderline if between 8 and 10, and abnormal if >10 [27]. At inclusion, 26.5% had abnormal values for anxiety and 26.5% had borderline values. Scores for depression were abnormal in 16.3% and borderline in 12.2%. There was no significant difference between groups at inclusion, and values remained stable without any difference between groups during longitudinal follow-up (Table 2, online suppl. Fig. 1S and 2S).

COPD Assessment Test

Average values were very high for both groups at inclusion (Table 2) reflecting severe impairment without any difference between groups at T0 or during follow-up. Globally, 88% had a CAT value >10.

Symptom Scores: Edmonton Symptom Assessment Scale

ESAS scores were performed only in the EPC group [30], being considered as inherent to the palliative symptom assessment. Values at T0 are provided in Table 4. Online supplementary Figure 11S shows individual items at inclusion and during follow-up. Highest values (i.e., worse) were recorded for the items "breathlessness," "fatigue," and "well-being." Symptom scores above 4 were recorded in 37.6% (67 of 178) of home visits but led to a specific medical intervention in 12 occurrences only (most suggestions of medical intervention being refused by patients).

Advance Care Planning

At inclusion, 3 patients in each group had completed their ACP directives (p = 1.000). At the end of the study, 9 patients (35%) of the EPC group versus 3 (13%) of the control group had completed ACP directives (p = 0.194).

Table 4. Edmonton Symptom Assessment (ESAS) scores at inclusion for patients in the intervention group (early palliative care; $n = 23$)

ESAS scores	Mean	SD	Values >4, %
Pain	1	1.5	10.7
Fatigue	2.6	2.2	28.7
Nausea	0.1	0.6	1.7
Depression	1.9	2.2	14.0
Anxiety	2.3	2.5	21.9
Sleepiness	1.1	1.6	4.5
Low appetite	1.7	2.4	8.5
Dyspnea	2.7	2.5	32.0
Well-being	2.5	1.8	25.8

Values are on a scale from 0 to 10. A threshold of 4 was used to propose a medical intervention by a specialist in palliative care, a primary care physician or a specialist.

There was therefore a significant difference in the number of patients who wrote their ACP directives in favor of the EPC group ($p = 0.023$).

Survival

During the follow-up (454 days [1.24 years; 95% CI: 382–525] in the EPC group vs. 425 days [1.16 years; 95% CI: 339–509] in the SC group; $p = 0.592$), 8 deaths occurred, 4 in each group. Survival did not differ between groups (log-rank test, $p = 0.913$).

Appreciation of Intervention Questionnaire

Six months after the end of the intervention, patients of the EPC group were asked if they had appreciated the home visits of the specialized nurse (18 responses, 17 approved), and whether the monthly visits of the specialized nurse had impacted on their quality of life (9, i.e. 50% approved, 6 did not know, 3 disagreed).

Discussion

To our knowledge, this pilot study is the first prospective randomized study of an early palliative care intervention at home, over a 1-year period, in severe COPD patients, most of whom were on LTOT, home NIV, or both. Patients were very symptomatic, with high CAT scores, markedly impaired HRQL (SF-36), and high levels of anxiety and depression. Palliative intervention was based on monthly interventions at home with a holistic approach. The study showed that recruitment in the targeted population was a major problem. As a result of this, data presented are underpowered to exclude any effect of the palliative care intervention. The intervention was feasible, as well as the evaluations performed of the use of health resources, HRQL, and emotional disorders. Data show a trend for a higher rate of hospital and ICU admissions for respiratory causes in the intervention group, which loses statistical significance when expressed as number of events per patient. Mood, HRQL, and CAT scores did not differ significantly between groups initially or during follow-up. However, more patients completed ACP directives in the intervention group.

Defining "early" intervention for palliative care is arbitrary [31]. We chose patients with LTOT and/or NIV and or hospitalized within the preceding year. Patients hospitalized for AECOPD are at high risk of subsequent readmission or post-discharge mortality; those under LTOT and/or home NIV also have a limited survival, justifying the chosen criteria. Other items such as FEV_1 <30% predicted, oxygen dependence, AECOPD in the previous year, comorbidities, decreased functional status are also helpful to identify high-risk subjects and should trigger discussions on ACP and end-of-life care [31]. However, the interindividual variability of the clinical course of COPD is a problem: even indices such as the BODE or ADO are poor predictors of mortality for a given individual [32, 33]. Tools such as the ProPal-COPD require further validation but seem promising for selecting patients at high risk of 1-year mortality [34].

Recruiting patients for this study proved to be very difficult: although screening was prolonged, extended to another hospital and to all pulmonary physicians in our area, we did not reach the target number of cases and only 15% of the targeted population was finally included. Several factors explain these difficulties. First, we realized that palliative care was perceived as frightening for many patients and negatively associated with end-of-life care. Although the study was presented as focusing on improving symptom control, we were transparent as to the nurses' training, and did not dissimulate their identity as palliative care specialists. There is clearly a negative connotation to "palliative care," which had an unfavorable impact on study acceptance, despite the detailed explanations provided. To avoid this, integrating palliative care into usual care and developing a palliative care culture and competence among the respiratory care team is an interesting option. Secondly, cognitive impairment was a problem: none of the patients from the geriatric ward could be included because of their low MMSE scores; a nonquantified number of subjects with probable cogni-

tive limitation were not included in the screening process; in those formally screened, close to 10% had an MMSE score <23. Excluding subjects with cognitive disorders was mandatory for the reliability of questionnaires and symptom scores included in the study protocol. Cognitive impairment is an underestimated and important problem in this group of patients: a recent study showed that less than 50% of severe COPD patients discussing end-of-life options retained full comprehension of the options after 24 h [35]. Several other groups have documented cognitive impairment in COPD under LTOT [36–41]. Thirdly, comorbidities (cancer, severe cardiac failure), and end-of-life were also limiting factors for inclusion. Finally, there was a high reluctance to participate in our study based on concepts such as "fear of being a guinea pig," "uselessness of the study for their care," or refusal of randomization, even in patients followed by our team. Further studies on this topic must anticipate these difficulties.

The expected impact of the ECP group on hospital, ICU and emergency ward admissions was not confirmed. In fact, despite a similar rate of hospital admissions in both groups during the year preceding this trial, there were more admissions to both ICU and the emergency wards in the ECP group during the observation period. This trend was not significant when results are expressed as number of events per patients. There is no obvious explanation for this finding. As mentioned, these findings must take into account the limited number of subjects. It shows, however, the need for quantifying the use of health resources in future larger studies on this topic.

A positive finding was the increased number of ACP in the EPC group. One of the goals of the intervention was indeed to have patients understand the prognosis of their disorder and the possible futility of aggressive end-of-life managements. Very little data are available on ACP in COPD; and available data show that ACP is surprisingly uncommon in this population [42–45]. Paradoxically, ACP obtained most often expressed the desire of CPR and maximal treatment, patients failing to acknowledge their prognosis and the natural history of their disease [46].

In previous studies of advanced COPD, and symptom-based interventions, dyspnea has been a major focus [18]. Among medications prescribed for symptom control, in spite of its documented efficacy, we noted a high reluctance expressed by patients to use oral morphine: only 4 patients in each group (16%) accepted opiates for improving control of dyspnea. Prescription of morphine did not increase during the study period in spite of repeated encouragement by the intervention group. Reluctance to use morphine by physicians and patients is well described in this setting [47].

Our results did not show any impact of early palliative care on mood disturbances or HRQL. These results must be put in perspective. (1) The number of subjects finally included was under the level established to avoid a type II error and thus the study was underpowered for a definite conclusion. However, detailed analysis of mood (HAD), HRQL (SF-36), and symptoms (CAT) (see online suppl. Fig. 1S–11S) shows a remarkable similarity of results between both groups without the smallest trend favoring the intervention. (2) The tools used to evaluate secondary endpoints of the intervention may have been less responsive than disease-specific HRQL tools. We considered that adding a disease-specific HRQL questionnaire would be too time-consuming for study patients, who were already burdened by a very thorough assessment. (3) Modalities of the intervention could be questioned. However, the nurses implicated all had several years of experience in palliative care. Their interventions were directly supervised by a palliative care physician, who discussed all cases with the specialized nurses and defined medical strategies whenever symptom scores were abnormal (ESAS items >4). The intervention was comprehensive, including regular symptom assessment and control, patient education, psychological support to patients and caregivers, and alternative approaches such as relaxation, reflexology, and massages. We therefore believe that the intervention was appropriately designed. (4) Modalities of usual care in these patients may have "diluted" the impact of the palliative care intervention: all patients under LTOT and/or NIV in our area receive regular home visits be specialized nurses; 37% of patients had home physiotherapy; 31% had home nurses for nonrespiratory treatments. One may therefore surmise that the implication of several different health care workers may have limited the benefit of the intervention. Indeed, among patients refusing to participate in the study, one of the reasons provided was the fear of too many health care workers invading their privacy. (5) Finally, patient recruitment may have influenced our results: the 15.6% of subjects included, with a normal MMSE score, without significant comorbidities, accepting the idea of a clinical study, may have a different resilience regarding their illness and may not require the type of support provided.

Acknowledging these limitations, it is also possible that this type of intervention is not in phase with the expectations of severe COPD patients. It is common knowledge that cancer has a poor prognosis, but prognosis of COPD is unclear for patients, and information provided

by physicians is probably insufficient. Based on their understanding of their illness, ACP limiting access to ICU or CPR for instance may not make sense for these patients. Severe COPD often have unreasonable expectations and tend to ignore or deny their prognosis. It is also possible that EPC must target specific subgroups of severe COPD: these patients have many different phenotypes with different impacts on symptoms. Larger studies are required to explore this possibility.

In summary, in this pilot study of patients with severe COPD, most of whom were under LTOT and/or home NIV, quality of life was markedly impaired, with considerable mood disturbance, and functional limitation. Recruitment proved to be a major barrier, with several possible explanations, many of which are related to the underlying pathology. A monthly home palliative care intervention by specialized nurses for 1 year, completing usual care, was feasible. The present study was underpowered to exclude a benefit from palliative care. Advance directives were provided more often in the intervention group. Because of the major impact of severe COPD on HRQL, and on the use of health resources, further studies are necessary and must be designed to take into account the recruitment problems encountered, the frequency of cognitive impairment and of comorbidities in this population, and possibly specific phenotypes for whom ECP should be privileged.

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Disclosure Statement

The authors have no conflict of interest to report regarding the present study.

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