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Integrated early palliative care for patients with newly diagnosed glioblastoma: The GLIOSUPPORT feasibility study

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Abstract

Background. Early palliative care improves the quality of life (QoL) and survival in patients with cancer; however, its effects in patients with glioblastoma remain unclear. The GLIOSUPPORT study assessed the feasibility (adherence; primary objective) of an early palliative care program integrated into the standard glioblastoma care pathway. Secondary objectives included the description of the patients' characteristics, QoL, and neuropsychological changes over time, end-of-life decisions, end-of-life treatments, and family carers' perceptions/experiences.

Methods. This interventional, prospective, longitudinal, feasibility study was conducted in a French comprehensive cancer center. Thirty-five patients with newly diagnosed glioblastoma were required to reach an adherence rate of 60%. Adherence was defined as going to 3 palliative care visits scheduled every 12 weeks. Baseline characteristics were compared in patients who did and did not adhere to the palliative care program. Minimal clinically important differences and cut-offs were used to quantify QoL changes.

Results. The adherence rate was 60% (95% CI [42.1%-76.1%]), indicating that the program was feasible. Visual disturbances, communication/initiation deficits, and anxiety were more frequent in the group that did not adhere to the program. Emotional and social functioning, pain, appetite loss, constipation, and headache increased over time (clinically significant differences), whereas neuropsychological disturbances did not change. Half of the participants identified a family proxy and 8.6% wrote advance directives. One month before death, 28.6% of patients were receiving cancer treatment.

Conclusions. Integrating early palliative care in glioblastoma management is feasible. The potential benefits on QoL, mood, and survival must now be evaluated in a larger randomized controlled trial.

Key Points

- Integrating early palliative care into glioblastoma management is feasible.
- We propose an integrated model for supportive care in newly diagnosed glioblastoma.
- The benefits on quality of life and survival of this interventional model must be assessed.

Glioblastoma is the most common primary malignant tumor of the central nervous system[1] (48% of all primary malignant brain tumors) and its incidence increases with age.[2] In France, there are ~2000 new cases per year.[3,4] Glioblastoma is 1.58 times more common in men than women, and the median age at diagnosis is 65 years. Different treatments can be offered to patients, including surgery, radiotherapy, and chemotherapy; however, there is no cure and the median overall

Importance of the Study

This prospective monocentric study demonstrated that integrating early palliative care in the glioblastoma care pathway is feasible, as reported for other incurable cancers. At adjuvant treatment initiation, palliative care visits and neuro-oncologic visits were scheduled alternately every 6 weeks. Many included patients had frailty, distress, and motor or language deficits. In these patients, neurocognitive impairments may affect their decision-making capacity and communication. Early palliative interventions might contribute to reduce anxiety/depressive symptoms, to improve quality of life, to better cope with the prognosis, and to facilitate communication about end-of-life-care preferences. The adherence rate of 60% (95% CI [42.1%–76.1%]) to the early palliative care program allows now to conduct a larger study to test whether this program improves the quality of life and survival in patients with newly diagnosed glioblastoma. This study might bring additional evidence to support an integrated care model for the management of patients with an incurable brain cancer.

survival is variable, but almost always less than 2 years after diagnosis.[5–8]Therefore, quality of life (QoL) is very important for these patients and their families. Most patients with glioblastoma, especially women, experience neurologic deficits, neurocognitive impairment, and physical symptoms that reduce autonomy and QoL.[9] Seizures are observed in 27% of patients at diagnosis and up to 50% during the disease course, and they strongly affect daily life.[10] Motor difficulties, insomnia, fatigue, and communication problems also reduce QoL.[11,12] Meyers et al.[13] showed that neurocognitive functions, which can be differently impaired according to the tumor localization,[14] might predict survival in patients with recurrent malignant glioma. Furthermore, patients with glioblastoma report mood disorders, higher levels of panic, depression, anxiety, and fear of death compared with patients with low-grade glioma.[11] This may lead to attention and motivation deficits that affect some neurocognitive domains and also QoL.[15,16] Several studies found a correlation between QoL deterioration and overall survival.[17,18] Family caregivers also report high distress levels.[2,19]They must cope with the fact that a loved one has an aggressive tumor that requires intense treatments in the first months after diagnosis and is characterized by a short time to progression.[2,5] Caregivers often feel unprepared for this, in term of information and training.[20] In this context, palliative care (PC) might improve the QoL of both patients and family caregivers by allowing the early identification, assessment, and management of pain and physical, psychosocial, neuropsychological, and spiritual problems.[21]

Palliative care is based on a multidisciplinary approach and advance care planning (ACP)[22] that allows patients and family caregivers to make informed choices. Currently, only 15%–40% of patients with glioblastoma receive a PC consultation at diagnosis or later during the disease course.[2,23–25]Yet, previous findings demonstrated the benefits of early PC on QoL, mood and at times, on survival in patients with systemic cancer.[26–28] A recent retrospective study investigated differences in the timing of PC integration (early vs. late vs. no integration) on various outcomes in patients with glioblastoma.[23] Survival and number of hospice claims were significantly different in the 3 groups. However, the authors could not assess causality. These differences could be due to the timing of PC integration, the patients' outcomes, and/or the healthcare resources. In another recent retrospective study,[29] patients without PC had greater odds of receiving oncological treatments for glioblastoma in the last months of life, without survival benefit, compared with those who received PC. Therefore, Wu and coworkers[23,25] recommended to carry out prospective studies and randomized controlled trials to collect valuable information on the impact of early PC integration in patients with glioblastoma.

The aim of this study was to assess the feasibility of integrating an early PC program into the standard glioblastoma care pathway.

Methods

Study Design

GLIOSUPPORT was an open interventional, prospective, longitudinal, feasibility study carried out at a French comprehensive cancer center. The study protocol, registered on clinicaltrials.gov NCT04516733, was approved by an Ethics Committee (*CPP-Est-II#18/07/23/34506*) and was conducted in accordance with the Helsinki Declaration and the Good Clinical Practice requirements.

Participants

Patients were included if older than 18 years, with newly diagnosed and histologically confirmed glioblastoma, and treated on site. Patients were not included if they could not provide a written informed consent before inclusion, had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 4, or were not affiliated with the French social security system. Designating a family caregiver was not an inclusion criterion. The family caregiver did not need to provide consent.

Procedure

After surgery/biopsy leading to the glioblastoma histological diagnosis in another hospital, patients were referred to our center for a neuro-oncological/radiotherapy consultation (screening visit). Patients were included if

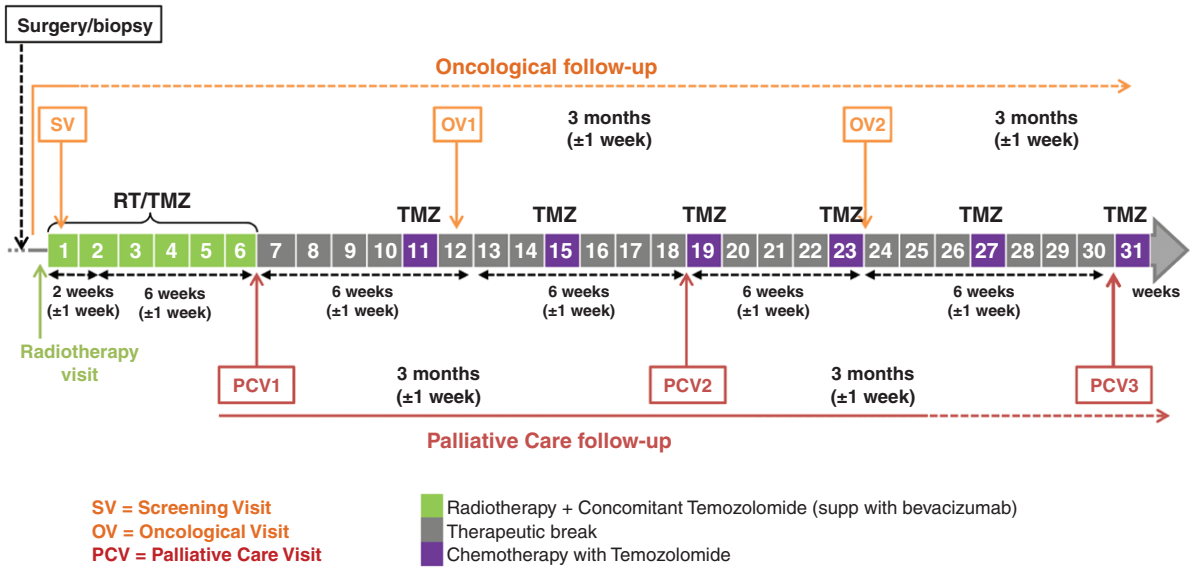

Figure 1. Diagram of the integrated management model for patients with glioblastoma treated with first-line radiotherapy and/or chemotherapy. (TMZ = temozolomide; RT = radiotherapy).

they met the inclusion criteria. During the study design meetings, oncologists said that they perceived the word "palliative" as more distressing and hope-reducing for patients/family caregivers compared with "supportive," as already observed in a previous study.[30] Thus, the term "palliative-supportive" was chosen to facilitate the early patients' referral to the PC team. Nevertheless, for clarity, the term "palliative" was used throughout the manuscript. After the screening visit, PC visits (PCVs) and oncological visits (OVs) were scheduled alternately every 6 weeks, starting with a PCV, for a total of 6 visits (3 OVs and 3 PCVs) (**Figure 1**). Oncological visits were scheduled according to the standard practice in France (ie, every 12 weeks). If patients missed an appointment (OV or PCV), they were contacted by telephone only to maintain the contact and to enquire about the reason for non-attendance.

Intervention

During the OVs (30 min/each), an oncologist (M.F. or A.D.) or a radiotherapist (M.C.) carried out the standard neuro-oncologic consultation.[2] Clinical data were collected, including general and neurological state, treatment tolerance, and daily routine.

Palliative care visits were interdisciplinary and multidisciplinary consultations based on relevant clinical practice guidelines.[31–36] Each PCV lasted 180 min and included systematically 3 core PC providers (i.e. a physician, a nurse, and a clinical neuropsychologist). Depending on the needs they identified, the patient could meet other PC providers (ie, psychodynamic psychologist, social worker, physiotherapist, dietitian, addictologist, or spiritual companion). The number, timing, and duration of the potential additional PC interventions were tailored to the clinician's discretion, but discussed and scheduled in coordination with the core PC team.

The core PC team (e.g., M.T., V.P., C.G., A.-C.G., P.C., L.C., and E.G.) was trained in palliative culture, care, and medicine through a specific university post-graduate diploma and a training course on the ethics and communication-enabling factors for ACP (e.g., ACP knowledge and attitudes, preferences, self-efficacy, and outcome expectancy beliefs). Two of the core physicians (M.T. and C.G.) were also pain management specialists. The clinical neuropsychologists (L.C. and E.G.) received formal university training in neurology and cognitive and behavioral therapy. The PC team skills in neuro-oncology (and the oncologists' skills in PC) were the results of their formal university training and also of their informal continuing training through their long-standing interactions at the hospital in weekly meetings, multidisciplinary consultations, and regular joint consultations that involve the patient, neuro-oncologist, and PC team (1–3 per month). Potential disagreements between the PC team and oncologists are addressed as often as necessary during these meetings.

The PCVs were not formally structured as a dedicated ACP program, but were based on an ACP communication model that integrates socioemotional processes, and were driven by PC practice guidelines.[22,31–33] Therefore, besides the specific neuro-oncological features, several factors were taken into account and discussed during the PCVs, including the patients and their relatives' tolerance for uncertainty (ie, several uncertainties emerge in end-of-life decisions), responses to moral dilemmas and ambivalences (ie, conflicting existential values in the end-of-life care), and emotional discomfort (ie, discussions about the potential impending death). Relational factors were also integrated into the PCVs, such as the history of the relationships between the involved persons, decision-making

preferences (this provides a greater opportunity to ensure that the patients' wishes are honored when they are no longer able to make decisions for themselves), communication experience, and satisfaction with care.

The PCV started with a physician and a nurse (M.T., C.G., or V.P. and A.-C.G.) who (1) built the relationship with the patients and family caregivers, (2) managed symptom, distress, and functional status (eg, pain, asthenia, mood, nausea, or constipation), (3) gave information and explanations about glioblastoma and its prognosis, (4) explained the treatment objectives, (5) assessed the coping and support needs, (6) proposed assistance with medical decision-making, (7) coordinated with or referred to other PC providers, and (8) explored uncertainties and emotional discomfort in end-of-life decisions. The physician and nurse also collected clinical data (symptom progression, detailed treatments, and tolerance) and the home experience with the family caregiver (a relative or a friend designated by the patient as the primary carer). Then, a trained clinical neuropsychologist (E.G. or L.C.) conducted a clinical interview based on an ACP communication model. She also used self-report and clinician-rated questionnaires and tests to assess the QoL, psychological distress, and neurocognitive function impairment. Based on the scores, items that deserved attention guided the patients' referral to specialists (eg, physical/psychological/social/spiritual support, speech therapy). The time necessary to score the clinician-rated neuropsychological tests and self-report questionnaires was not included in the consultation time.

In line with the PC culture and the Response Assessment in Neuro-oncology (RANO)-Cares working group,[31,37] family caregivers also had the opportunity to meet a psychodynamic psychologist (P.C.), a social worker, or other care providers (eg, for physical, psychological, or spiritual support). As the knowledge of the possibility to write advance directives (ADs) is a significant predictor of AD completion,[38] patients received a brochure on AD that was designed based on the Physician Orders for Life-Sustaining Treatment (POLST) documentation.[39]

Measures and Outcomes

Feasibility (the primary outcome) was defined as the percentage of patients who adhered to the PC program (ie, patients who went in person to the 3 scheduled PCVs with the 3 core providers). The feasibility threshold was predefined as a PCV completion rate ≥ 60%, on the basis of the glioblastoma population's disability level and previous studies that highlighted significant challenges in recruitment, retention, and compliance with the study procedures.[40]

Secondary descriptive outcomes were:

1/ Longitudinal assessment of QoL with the self-report 30-item European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30),[41] which includes 5 functional scales, 9 symptom scales, and a global health status scale, and with its brain cancer-specific module BN20,[42] which has 20 items grouped in 11 symptom scales.

2.1/ Psychological distress, assessed using the Hospital Anxiety and Depression Scale (HADS),[43,44] a valid, simple, sensitive tool for screening psychiatric disorders in oncological populations. It is a 4-point, 14-item self-report questionnaire that provides a global score and also 2 sub-scores for anxiety and depression.

2.2/ Global neurocognitive functioning, assessed using the clinician-rated Mattis Dementia Rating Scale (DRS).[45] This widely used and well-accepted cognitive test for populations with neurologic disorders[46] has been designed to provide an overall score based on several cognitive tasks. Age- and education-corrected norms allow defining some global deficit cut-off scores. The test contains 5 subscales where items are presented in a hierarchical manner. Its administration takes 10–15 min in healthy persons and 30–45 min in severely impaired patients.

3/ Decisions about end-of-life, collected through a semi-structured interview and summarized as the number of patients who designated a trusted person (i.e. a healthcare proxy) after the diagnosis and wrote their AD. The definitions of "trusted person" and "AD" in France are detailed in Supplementary Table S1.

4/ The family caregivers' experiences/perceptions, explored through a clinical interview and characterized by the type of home/work situation, relationship with the patient, and psychological state/support.

5/ The Index of Independence in Activities of Daily Living (ADL)[47] was filled in by the patients and their families, to assess the patients' autonomy at home and to describe healthcare needs. It evaluates 6 basic daily activities.

6/ Adverse events induced by the anticancer treatments, graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). Only grade ≥ 3 toxicities were recorded for this study. The efficacy assessment was based on the RANO criteria.[48] Follow-up MRI was performed every 12 weeks (ie, OV1, 2, and 3) and results were compared with those of the post-operative MRI (baseline).

Statistical Analysis

The sample size calculation was based on the feasibility indicator (percentage of patients who adhered to the PCV program). Thirty patients would allow estimating an adherence rate of ~60% with a 95% confidence interval (CI) width of 0.34. Considering 15% of patients potentially not coming to any PCV (non-evaluable patients), 35 participants were required. The percentage of patients who adhered to the PCV program (primary endpoint) was presented with the 95% CI, estimated with the exact binomial method. The QLQ-C30 and BN20 scores were calculated following the EORTC guidelines. The within-group minimal clinically important differences (MCIDs)[49] were used to quantify the presence of significant score changes at PCV2 and PCV3 compared with PCV1 (baseline). A 10-point change threshold was used for BN20 score changes.[50] The HADS and DRS were scored according to the French guidelines and recommendations.[44,51]

Categorical variables were described with frequencies and percentages, and continuous variables with means, medians, and ranges. No imputation method was used for

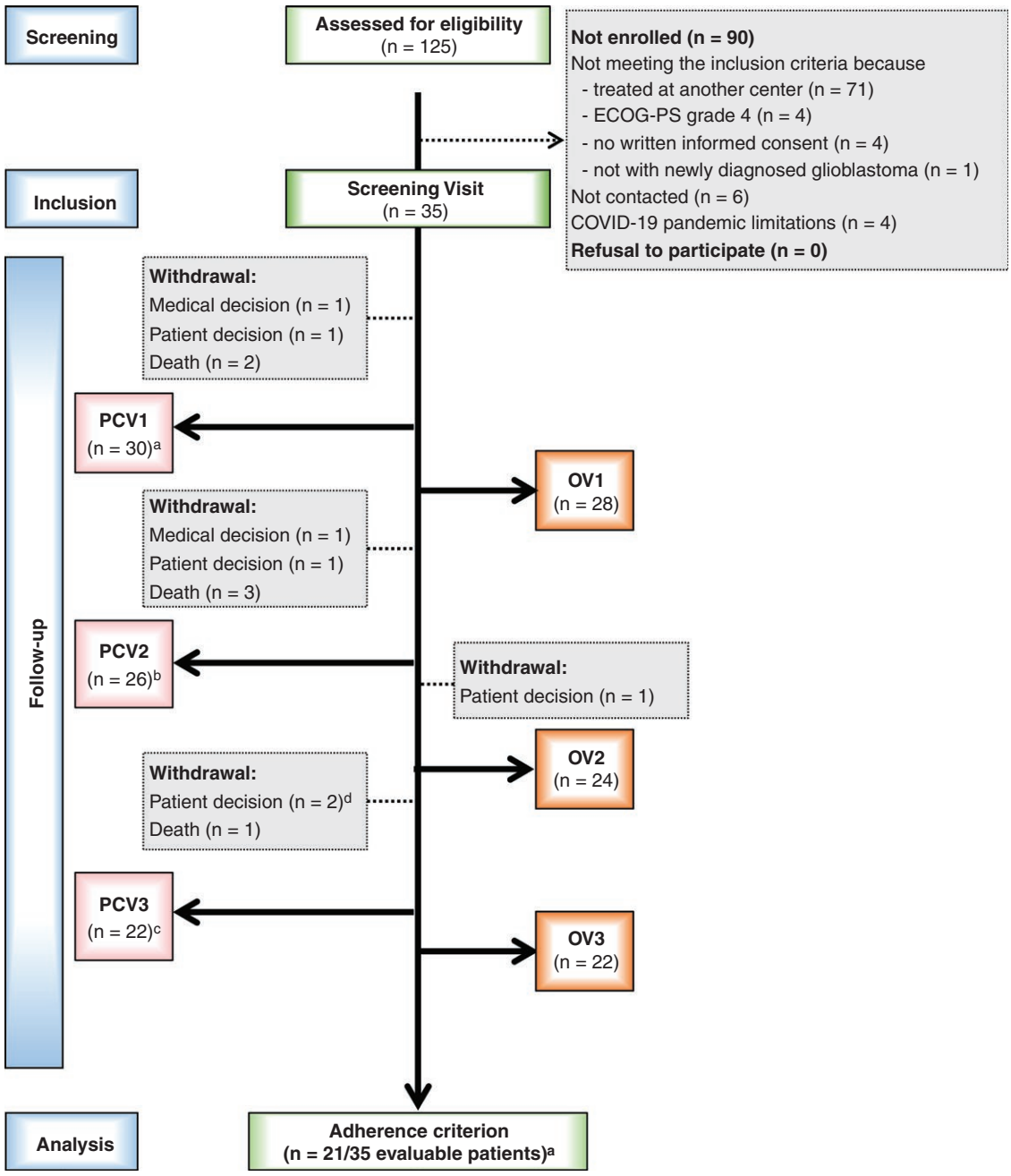

Figure 2. CONSORT flowchart of patients' inclusion and patients' adherence to the program. PCV = Palliative care visit; OV = Oncological visit; ECOG PS = Eastern Cooperative Oncology Group performance status; a One patient missed PCV1 (but completed OV1); b Three patients (who missed OV1) completed PCV2; c One patient who missed OV2 attended PCV3. d All patients who withdrew their consent during the study allowed the use of their data.

missing data. Quantitative variables were compared using the non-parametric Kruskal–Wallis test or the Wilcoxon signed rank test for comparing different time points. Categorical variables were compared with the chi-square test. Comparisons were carried out only for exploratory purposes. The median follow-up was estimated using the reverse Kaplan–Meier method. Survival was calculated from the date of inclusion to the date of death or of last follow-up (censored data). Data were analyzed using Stata, version 16 (StataCorp LP, College Station, TX).

Results

Study Participants

From May 2019 to September 2020, 125 patients with glioblastoma were screened (**Figure 2**). As 90 (72%) did not meet the inclusion criteria (56.3% treated at another hospital), 35 participants were included in the study (median time from diagnosis to inclusion: 1.3 months, range 0.5–2.5).

Table 1. Participants' Characteristics at Baseline

Characteristics	*N* = 35	%
Sociodemographic features		
Age (years)		
Median (range)	62 (31; 82)	
Sex		
Male	23	65.7
Female	12	34.3
Years of education		
Median (Range)	11 (6; 17)	
ECOG[a] performance status		
0–1	28	82.5
2–3	6	18
Surgery		
Biopsy	11	32.4
Resection	24	68.6
-Total	8	47
- Subtotal	3	17.6
-Partial	6	35.3
-Missing	6	
Histomolecular diagnosis (WHO 2016)[b]		
Glioblastoma, IDH-wild type	35	100
Tumor MGMT[c] promoter methylation status		
Unmethylated	18	54.8
Methylated	15	45.2
Missing	2	
Neurological deficits[d]		
Motor	15	42.9
Speech disorder	9	25.7
Sensory	8	22.9
Visual disturbances	6	17.1
Sign of intracranial hypertension	6	17.1
Cognitive	5	14.3
Sleep disorders	5	14.3
Partial epileptic seizures	4	11.4
Behavioral disorder	2	5.7
Generalized epileptic seizures	1	2.9
Physio-neuro-psychological disorders		
Asthenia/Fatigue	10	28.6
Anxiety-depression symptoms	7	20.0

[a]ECOG = Eastern Cooperative Oncology Group performance status.
[b]Refers to the 2016 WHO classification of tumors of the central nervous system published by Louis et al. (2016). There is a more recent (Louis et al., 2021) WHO classification, but we used the old one because the diagnoses were done before the new classification.
[c]O-6-methylguanine-DNA methyltransferase.
[d] Using clinical observations.

Their baseline characteristics are summarized in **Table 1**. After surgery, 34/35 participants (97.1%) received first-line radiotherapy (for a median of 6 weeks) and temozolomide, and then temozolomide alone as maintenance therapy (for a median of 9.5 weeks). One patient began temozolomide, but worsened quickly, thus did not receive radiotherapy. At inclusion, the most common concomitant treatments were corticosteroids (70.4%), antiepileptics (63%), antidepressants (18.5%), anxiolytics (14.8%), and analgesics (14.8%). At recurrence, bevacizumab was used as second-line treatment in 17 patients (48.6%) and lomustine in 3 patients. Ten patients experienced chemotherapy-related-toxicities (grades 3–4 according to the NCI-CTCAE criteria): thrombocytopenia ($n = 7$), neutropenia and anemia ($n = 1$), lower limb edema ($n = 1$), and weight gain with asthenia and drowsiness ($n = 1$).

Feasibility (Primary Outcome)

Among the 35 included patients (intention-to-treat sample), 21 went in-person to all 3 PCVs (ie, adherence criterion). Therefore, the adherence rate was 60% (95% CI [42.1%–76.1%]). Specifically, 86%, 74%, and 63% of the 35 patients went to PCV1, PCV2, and PCV3, respectively (Figure 2). Reasons for non-adherence ($n = 14/35$, 40%) were: death ($n = 6$), withdrawal due to medical decision ($n = 2$), consent withdrawal ($n = 5$ because of: lack of time, worsening performance status, and distance from the center), and missed PCV1 ($n = 1$). The median time from diagnosis to PCV1 was 2.7 months [1.1–3.6].

The psychodynamic psychologist was present at 10%, 4%, and 13.6% of PCV1, PCV2, and PCV3, respectively, and the social worker at 10%, 4%, and 9%, respectively. The type and number of other PC interventions triggered by the PCVs were not collected.

Secondary Outcomes

Quality of life (whole population, n = 35).—The QLQ-C30 score analysis showed that the global health status score did not change over time ($P = .195$), whereas the pain and constipation scores significantly increased ($P = .008$ and $P = .036$) (**Table 2**). Using the MCID, these changes were significant between PCV1 and PCV3 (and between PCV1 and PCV2 for pain). Using the MCID, dyspnea, appetite loss, and role functioning were worse at PCV3 than at PCV1 (**Table 2**).

In the BN20, only the headaches score significantly ($P = .031$) and clinically (MCID) increased over time. Conversely, the hair loss score was lower (clinical improvement) at PCV3 than at PCV1.

Neuropsychological functioning.—The HADS total score (**Table 3**) tended to increase over time ($P = .07$), suggesting more distress. The HADS anxiety score improved at PCV2, but increased again at PCV3 ($P = .05$). However, the percentage of patients with clinically significant psychological distress (HADS total score ≥ 13) did not change over time: 42.8% at PCV1, 36.4% at PCV2, and 50% at PV3 ($P = .65$).

The DRS total score (Table 3) did not change over time ($P = .60$) as well as the percentage of patients with significant global cognitive impairment (DRS total score < 136 or 129 according to age- and education-corrected norms):

Table 2. Changes in Quality of Life (Using the EORTC QLQ-C30 and BN20 Questionnaires) between Palliative Care Visits (PCVs)

	PCV1 (*n* = 30)		PCV2 (*n* = 26)			PCV3 (*n* = 22)			
	Mean	SD	Mean	SD	*Mean difference[a] (MCID)*	Mean	SD	*Mean difference[a] (MCID)*	*P*[b]
EORTC QLQ-C30									
Global health status	66	16.87	65	23.84	*–1*	63	15.87	*–3*	0.195
Physical functioning	76	21.75	72	25.74	*–4*	71	24.74	*–5*	0.131
Role functioning	66	32.55	64	35.05	*–2*	57	33.51	***–9***[c]	0.267
Emotional functioning	68	21.07	77	24.01	***9***[b]	74	23.71	***6***[b]	0.459
Cognitive functioning	75	25.46	75	24.53	*0*	76	21.95	*1*	0.330
Social functioning	62	32.03	72	28.82	***10***[b]	72	28.66	***10***[b]	0.106
Fatigue	49	28.28	43	32.39	*–6*	47	25.64	*–2*	0.373
Nausea and vomiting	5	14.24	5	10.52	*0*	8	18.32	*3*	0.375
Pain	10	13.17	22	28.70	***12***[c]	27	29.32	***17***[c]	**0.008**
Dyspnea	21	26.00	16	29.93	*–5*	30	35.71	***9***[c]	0.766
Insomnia	33	33.95	23	27.40	*–10*	22	31.11	*–11*	0.590
Appetite loss	17	30.77	18	26.68	*1*	25	35.66	***8***[c]	0.289
Constipation	32	37.53	30	35.50	*–2*	55	39.40	***23***[c]	**0.036**
Diarrhea	4	10.50	5	15.59	*1*	15	27.52	*11*	0.156
Financial difficulties	11	27.30	12	26.32	*1*	8	21.29	*–3*	0.500
Missing. n	*2*		*4*[b]			*2*			
EORTC QLQ-BN20									
Future uncertainty	30.32	22.30	24.75	23.88	*–5.57*	33.33	26.79	*3.01*	0.307
Visual disorder	14.81	18.73	14.14	16.86	*–0.67*	12.28	12.22	*–2.53*	0.367
Motor dysfunction	27.31	28.37	23.23	25.87	*–4.08*	20.47	20.04	*–6.84*	0.855
Communication deficit	22.22	27.22	20.71	28.13	*–1.51*	18.13	28.26	*–4.09*	0.844
Headaches	9.72	18.33	21.21	26.32	***11.49***[c]	28.07	29.94	***18.35***[c]	**0.031**
Seizures	1.39	6.80	1.52	7.11	*0.13*	0	0.00	*–1.39*	1.000
Drowsiness	31.94	20.80	30.3	28.93	*–1.64*	29.82	26.98	*–2.12*	0.727
Itchy skin	22.22	33.57	27.27	35.09	*5.05*	12.28	19.91	*–9.94*	0.250
Hair loss	25	40.82	24.24	32.82	*–0.76*	10.53	24.98	***–14.47***[c]	0.250
Weakness of legs	25	28.23	22.73	33.15	*–2.27*	26.32	30.59	*1.32*	0.645
Bladder control	18.06	27.77	24.24	29.42	*6.18*	15.79	28.04	*–2.27*	1.000
Missing. n	*6*		*4*			*3*			

SD: Standard deviation; MCID: Within-group minimal clinically important differences according to Dirven et al. (2021)
[a]Difference from PCV1 (ie, difference = mean score at PCV2 or 3—mean score at PCV1).
[b]Better level of functioning (improved quality of life according to the MCID).
[c]Worse level of functioning or worse symptoms (deteriorated quality of life according to the MCID).
[d]Wilcoxon signed rank test. See **Figure 2** for explanations of the number of patients at each PVC.

64.3%, 68.4%, and 57.9% ($P = .79$). Initiation was the neurocognitive domain that deteriorated more over time.

End-of-life decisions.—In total, 19/35 patients (54.3%) identified a trusted person (14 of these patients went to all 3 PCVs): 12 patients at PCV1, 3 at PCV2, and 4 at PCV3. Only 3 patients (8.6%) wrote their AD: 2 at PCV1 and 1 at PCV2.

The announcement of disease progression or of cancer treatment withdrawal to the patient and family was given during an OV or a PCV (for adherent patients; in the presence of the neuro-oncologist).

Patients' situation at home and family caregivers' experiences.—All 35 patients lived at home. The ADL index (Table 4) showed that ~80% of patients remained autonomous. The percentage of patients who received care from another home-based PC network increased from 3.3% (PCV1) to 27.3% (PCV3) ($P = .008$). They mostly received support at home from the general practitioner, nurses, physiotherapists, and speech therapists (**Table 4**). Most family caregivers lived at home with the patient (the partner in 90% of cases). Among the family caregivers who were still working (~30%), 30% had reduced their working time. Moreover, 25%–50% of family caregivers

Table 3. Neuropsychological Changes, Including Psychological Distress (HADS) and Neurocognitive Functioning (Mattis DRS) at the Different Palliative Care Visits (PCVs)

	PCV1 (*n* = 30)			PCV2 (*n* = 26)			PCV3 (*n* = 22)			*P*[b]	*P*[c]
	Mean (SD)	Min; Max	Significant[a] *n* (%)	Mean (SD)	Min; Max	Significant[a] *n* (%)	Mean (SD)	Min; Max	Significant[a] *n* (%)		
HADS											
Anxiety	6.5 (3.9)	(0; 17)	**12 (42.9)**	5.5 (3.8)	(0; 12)	**6 (27.3)**	6.8 (3.7)	(0; 16)	**9 (45.0)**	0.049	
Depression	6.3 (4.3)	(0; 14)	**10 (35.7)**	6.1 (5.0)	(0; 20)	**6 (27.3)**	7.3 (4.1)	(1; 17)	**8 (40)**	0.112	
Total score	12.8 (7.2)	(1; 26)	**12 (42.8)**	11.6 (7.9)	(0; 26)	**8 (36.4)**	14.1 (7.2)	(4; 33)	**10 (50.0)**	0.070	**0.650**
Missing, n		*4*			*4*			*2*			
Mattis DRS											
Attention	35.0 (1.4)	(32; 37)	**0 (0.0)**	35.0 (1.9)	(30; 37)	**1 (5.6)**	35.1 (1.9)	(31; 37)	**2 (10.5)**	0.304	
Initiation	30.5 (5.4)	(20; 37)	**8 (29.6)**	28.3 (8.2)	(5; 37)	**7 (36.8)**	30.7 (6.7)	(15; 37)	**6 (31.6)**	0.465	**0.836**
Construction	5.9 (0.4)	(5; 6)	**0 (0.0)**	5.6 (0.9)	(3; 6)	**2 (10.5)**	5.9 (0.3)	(5; 6)	**0 (0.0)**	0.564	
Conceptualization	34.9 (3.7)	(21; 39)	**2 (7.4)**	36.0 (3.0)	(30; 39)	**2 (11.1)**	35.3 (4.0)	(26; 39)	**3 (15.8)**	0.515	
Memory	22.1 (2.9)	(14; 25)	**1 (3.7)**	21.8 (2.6)	(17; 25)	**3 (16.7)**	21.4 (3.1)	(15; 25)	**4 (21.1)**	0.154	
Total score	128.4 (9.9)	(100; 144)	**18 (64.3)**	128.1 (9.6)	(103; 141)	**13 (68.4)**	128.5 (12.5)	(99; 144)	**11 (57.9)**	0.604	**0.793**
Missing, n		*2*			*7*			*3*			

SD: Standard deviation; HADS: Hospital Anxiety and Depression Scale; DRS: Dementia Rating Scale
[a]Refers to a clinically significant score (i.e. a score that is equal or inferior to a cut-off aligned to guidelines and norms).
[b]Wilcoxon test for paired samples.
[c]Chi-square test to compare the percentage of patients whose score was classified as significantly different between visits. See Figure 2 for explanations of the number of patients at each PVC.

Table 4. Patients' Management at Home and Family Caregivers' Situation at the Different Palliative Care Visits (PCVs)

Home situation	PCV1 (*n* = 30)		PCV2 (*n* = 26)		PCV3 (*n* = 22)	
	N	%	*N*	%	*N*	%
Patient' Index of Activities of Daily Living (ADL)						
Score ≤ 5 (dependence)	5	17.9	5	20	3	13.6
Score > 5 (autonomy)	23	82.1	20	80	19	86.4
Missing	*2*		*1*			
Intervention of supportive care providers at home						
Home-based palliative care team	1	3.33	1	3.84	6	27.3
Family physician	17(/29)	58.6	15 (/26)	57.7	11	50
Nurse	10	33.3	7(/25)	28	6	27.3
Physiotherapist	8	26.7	7(/25)	28	7	31.8
Occupational therapist	0	0	0(/25)	0	0	0
Speech therapist	2	6.7	1(/25)	4	2	9.1
Psychologist	0	0	3(/25)	12	3	13.6
Alternative medicine	1	3.3	1(/25)	4	3	13.6
Family caregiver's situation						
Living at home with the patient	20	66.7	19	73.1	18	81.8
Currently working	6(/20)	30	5(/19)	26.3	5(/18)	27.8
Having recently reduced their working time	1(/20)	5	8(/19)	42	8(/18)	44
Feeling overburdened[a]	6(/20)	30	8(/19)	42	8(/18)	45
Receiving psychological care	5(/20)	25	8(/19)	42	9(/18)	50

[a]According to the palliative care team's clinical appreciation. See **Figure 2** for explanations of the number of patients at each PVC.

received psychological care because they felt emotionally overburdened.

Characteristics of adherent vs. non-adherent patients.—At baseline, exploratory analyses (Supplementary Table S2) showed that the ECOG-PS score tended to be worse in non-adherent ($n = 14$) than adherent ($n = 21$) patients (35.7% and 5% had a score of 2–3, respectively). The number of patients with visual disturbances was higher in the non-adherent than adherent group (5 vs 1).

At PCV1, the QLQ-C30 Emotional functioning and Cognitive functioning scores tended to be lower in non-adherent patients. The mean BN20 Communication deficit score was higher in non-adherent than adherent patients (43.1 ± 32.8 vs 11.8 ± 17) as well as the mean HADS score (9.0 ± 4.6 vs 5.5 ± 3.1), whereas the mean DRS Initiation score was lower (27.3 ± 5.5 vs 31.9 ± 4.9) (Supplementary Table S2).

Late cancer treatments.—According to the RANO criteria (in which the reference was the baseline, post-surgery MRI), at OV3 (i.e. after 6 cycles of temozolomide), 4 patients (11.4%) had a partial or complete response to first-line treatment, 8 (23%) had stable disease, and 9 (25.7%) had disease progression (data missing for 1 patient).

During the study period, 14 patients (40%) died and 4 of them (28.6%) received cancer treatment in the month before death. The cause of death was disease progression in 12 patients (85.7%) (unknown reason in 2). Nine patients died at a healthcare center (64.3%) that was a PC unit for 7. Among the 20 patients who died during the study period, 6 died after the screening visit and before PCV3/OV3 (**Figure 2**). Moreover, 7 of the 22 patients who went to PCV3 died after a median time of 5.2 months (range: 2.3–7.1). Therefore, at the study end, 15 patients were still alive.

The median follow-up (estimated with the reverse Kaplan–Meier method) was of 8.6 months (95% CI [8.3–9.3]).

The median overall survival at the study end was 11.3 months (95% CI [9.5–13.0]). The overall survival rates were 88.1% (95% CI [71.4–95.7]), 84.9% (95% CI [67.3–93.4]), and 74.8% (95% CI [51.9–87.9]) at 3, 6, and 9 months, respectively (Supplementary Figure S1).

Discussion

To our knowledge, this is one of the first prospective studies showing the feasibility of integrating non-structured PC early into the standard glioblastoma management. The adherence rate of 60% indicates that the feasibility requirements were met, and that on the basis of the estimated 95% CI, an adherence rate between 42% and 76% by patients with newly diagnosed glioblastoma could be expected. This is in line with the trial by Temel et al.[27] where compliance (defined as at least 50% of participation

in PCV) was 86% in patients with newly diagnosed metastatic lung cancer.

The median overall survival was < 1 year, similar to what was observed in real-life populations,[3] but shorter than what was reported in a highly selected population.[7] The fact that total or subtotal resection could be performed only in 34.4% ($n = 11$) of patients explains the poor prognosis for a significant proportion of the sample. In the month before death, 4 patients (28.6%) received a specific cancer treatment. This percentage is higher compared with other studies (between 6% and 17%).[52,53]

Another study on patients with metastatic cancer showed that early PC interventions significantly decreased the use of cancer treatments in the last month of life (52.5% vs 70%, $P = .05$).[31] Moreover, a retrospective study at an academic hospital with palliative and end-of-life care services found that only 17% of patients with glioblastoma received chemotherapy in their last month of life.[52]

Our exploratory results show that non-adherent patients had more visual, communication, initiation, and/or anxiety problems than adherent patients. Despite the small sample size, there are several lessons to be learned. As PCVs require a significant level of patient engagement to be successful, it is important to find the optimal way of integrating PC early in the glioblastoma care pathway, especially for patients with severe physical symptoms and initiation deficits who may benefit more from early PC. Patients with this profile should be screened using relevant tools[54] (ie, the intervention may be too burdensome for patients with increased symptom load, and should include fewer scales, assessments, and shorter neurocognitive testing, not to become counterproductive). Then, they should be integrated into pharmacological and non-pharmacological protocols to treat anxiety and cognitive disorders,[14] and/or addressed to ambulatory/home-based supportive care.[19] Moreover, early PC may be more effective if targeted to the patients' specific needs.[55] In our clinical experience, patients are more receptive when PC is described as "an extra layer of support." The QoL score analysis showed that pain, constipation, dyspnea, appetite loss, role functioning loss, and headaches clinically increased over time. Quality-of-life deterioration during glioblastoma progression is not surprising due to the extensive symptom burden and dismal prognosis. Another longitudinal study in the first year after diagnosis found a correlation between QoL score deterioration and glioblastoma progression.[56] Headache is a common symptom of brain tumors (4%–62% of patients).[32] Another study reported fatigue and financial difficulties at month 7 post-diagnosis.[14] This was not the case in our sample, suggesting that QoL changes may be heterogenous among patients with glioblastoma and/or that our concomitant interventions influenced the patients' QoL. The lack of control arm and adequate design does not allow drawing conclusions about the intervention efficacy.

The percentage of patients with significant neurocognitive impairment or distress did not change over time. The patients still alive at the last PCV may not have been very close to end-of-life (35.8% died after a median of 5 months following this visit, and then follow-up for this study was stopped according to the protocol). This is consistent with a previous study ($n = 42$ patients with glioblastoma) that found a stable cognitive summary score until relapse.[14] The unchanged neurocognitive test scores could be explained also by a "learning effect" because the same tool was used at all 3 PCVs. In addition, a recent prospective study[57] on symptoms and QoL in patients with glioblastoma and high-grade glioma at the end of life found that memory impairment, which was high at baseline, was one of the very few symptoms that did not increase significantly. Lastly, corrective actions triggered after the PCVs (eg, speech/neurocognitive/psychological therapy) also may have contributed to the neurocognitive stabilization. The lack of a control arm and data on these corrective interventions does not allow for confirmation of this hypothesis. In the study by Flechl et al.,[14] verbal fluency was worse in patients with left-sided than right-sided tumors. In our sample, verbal initiation was the most frequently impaired domain, whatever the tumor localization. Neurocognitive alterations may also affect the decision-making capacity and thus the capacity to provide informed consent to the treatment options proposed by physicians. In our sample, about half of the patients had significant neurocognitive impairment at PCV3. As recommended, screening neurocognitive functioning could help to identify patients with impaired decision-making capacity who should then undergo further evaluation using a validated capacity assessment tool.[58] Psychological distress remained stable over time and concerned ~50% of participants (45% reported anxiety and 40% depressive symptoms). This is higher than in a recent and larger cohort of patients with different glioma types (24% with anxiety and 17% with depressive symptoms, using the same scale).[59] However, our sample was more homogeneous and smaller. Nevertheless, the management of symptoms, such as mood and behavioral disorders and neurocognition impairment, is essential to improve the QoL and reduce the symptom burden.[33]

More than half of the included patients (19/35) identified a family caregiver, but only 3 wrote their ADs. This may be explained by the fact that the PCVs were not formally structured as an ACP program. Awareness about the possibility of writing AD is a significant predictor of AD completion, but it is not enough because some patients may need help to carry out this procedure. Most family caregivers lived at home with the patient: one-third of them reduced their working time and many seemed overburdened and in need of psychological care. This is consistent with 2 studies on the caregivers' QoL, challenges, and emotions at the end of life in the context of glioblastoma[14,40] where 50% of family carers reported job restrictions that affected their caregiving capacity, 29% felt incompletely prepared for their tasks, and 29% complained about financial difficulties. Family caregivers are often torn between a strong engagement in caring and burnt-out symptoms.[40] Integrating PCVs in the cancer care pathway could help family caregivers to deal with these issues, to provide effective social support, to elicit patient decisional needs, and to explore and enhance decision-making conversations.

Our study wanted to test an integrated care model for the management of adverse events throughout the cancer trajectory. Based on the existing empiric and conceptual models,[34–36] we propose an integrated framework for PC in glioblastoma. Oncologists (neuro-oncologists and radiotherapists) have a crucial role in proposing PC. They

are trained in the management of glioblastoma-related complications and cancer treatment side effects, but cannot assume the entire burden of care because of time constraints. While it is recognized that PC should be an integral part of neuro-oncology training, many providers still do not feel comfortable.[60,61] Our model proposes a collaborative teamwork where different specialists bring their unique expertise. This model offers many benefits to clinicians (building progressive therapeutic alliances, taking care of both patients and family caregivers, helping to cope with the disease while undergoing cancer treatment). At our center, early PC has been integrated into the care pathway of patients with newly diagnosed glioblastoma.

Some limitations of this study deserve comment. First, the sample size was small, and the definition of adherence was very restrictive (attendance to 3 PCVs; patients who died before the third PCV were considered as nonadherent). However, our participants' sociodemographic and medical characteristics are consistent with those of patients enrolled in clinical trials,[5,62] and the adherence cut-off was chosen based on the glioblastoma literature. This restrictive definition may also strengthen the model generalizability and the expected adherence. Second, 14% of patients withdrew their consent. The reasons given by patients/family caregivers included not only the extra consultation time for the PCVs but also the worsening performance status and the distance from the center. Third, this feasibility study was not powered to determine PC efficacy. Besides demonstrating the PC intervention feasibility, the real strength of this study is the description of glioblastoma burden. Also, the psychiatric history and the mood disorder treatments were not collected longitudinally. Thus, QoL and neuropsychological functioning changes over time must be interpreted with caution. Fourth, assessing the family caregivers' distress using objective tools would have brought additional information. Fifth, integrating PCVs into the usual care pathway requires time, human resources, coordination, and motivation. This organizational aspect and its cost were not evaluated, although they could be barriers or challenges to the program implementation. Sixth, the 3 PCVs scheduled in addition to the conventional management might have been perceived as constraining by frail patients due to their duration. However, most assessments were conducted by an expert clinical neuropsychologist. Patients received no feedback or assistance while completing the self-report questionnaires during the PCVs. As reported for patients with low-grade glioma,[63] the clinical interviews and the feedback after test scoring might allow them to express their neuropsychological concerns in their own words, have their emotions acknowledged with empathy and respect, and receive appropriate responses from a trained clinical psychologist. These relational aspects may be beneficial for the patient. Moreover, corrective actions were put in place in function of the PCV outcome. This may have helped to cope with the PCV duration and most patient-family caregiver pairs found it acceptable. Furthermore, the prolonged sessions were in line with the neuropsychology practice at many cancer centers, such as the University of Texas MD Anderson Cancer Center.[64] However, this issue should be explored in future studies using post-intervention semi-structured interviews. Lastly, PCVs were not formally structured as an ACP program. They were conducted based on an ACP communication model that also integrated socioemotional processes. Future studies should focus on ACP as an important outcome. Data on the initiation of psychiatric treatments should also be collected as well as the number and the type of PC interventions triggered by the PCVs.

To conclude, this prospective study demonstrated the feasibility of integrating PC early in the management of patients with newly diagnosed glioblastoma. It might contribute to improve QoL, reduce anxiety/depressive symptoms, and improve coping with the prognosis and communication about end-of-life-care preferences. These findings might support an integrated care model for the management of patients with this incurable cancer. The potential benefits observed on QoL, mood, or survival must now be confirmed in a larger randomized controlled trial.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

glioblastoma | early palliative care | adherence | feasibility

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Disclosures

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) at

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Author Contributions

M.F., A.D., V.P., M.T., and E.G. designed the study and implemented it. M.J. performed statistical analyses and E.G. deepened them. E.G. drafted the first manuscript; M.F., M.T., A.D., and A.-C.G. drafted and revised the manuscript critically for important intellectual content. All the authors contributed to data collection. All authors critically reviewed and approved the latest version for submission.

Data Sharing

De-identified participant data will be made available upon request. Only requests that have a methodologically sound proposal will be considered. Proposals should be directed to the corresponding author; to gain access, data requestors will need to sign a data access agreement.

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