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BMJ Open Reasons for acceptance and refusal of early palliative care in patients included in early-phase clinical trials in a regional comprehensive cancer centre in France: protocol for a qualitative study

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ABSTRACT

Introduction A few studies have highlighted the potential synergy between early palliative care and inclusion in an early-phase clinical trial that may improve quality of life, reduce symptoms of exhaustion related to the side effects of treatment and allow patients to complete their treatment protocol. The primary objective of this qualitative study is to evaluate the reasons for acceptance or refusal of early palliative care in patients included in early-phase clinical trials.

Method and analysis All patients from the Centre Léon Bérard (Comprehensive Cancer Centre in Lyon, France) who consent to one of the early-phase clinical trials proposed at the centre will be invited to participate in this study. The cohort will consist of a subgroup (n=20) of patients who accept palliative care together with their clinical trial, and a second subgroup (n=20) of patients who decline it. Patients will be interviewed in exploratory interviews conducted by a psychology researcher before the start of their clinical trial. The interviews will be audio-recorded. Patients will also be asked to complete quality of life and anxiety/depression questionnaires both before the beginning of the treatment and at the end of their clinical trial. The content of the interviews will be analysed thematically. Descriptive and comparative statistical analysis of both cohorts will also be conducted.

Ethics and dissemination Personal data will be collected and processed in accordance with the laws and regulations in force. All patients will give informed consent to participate. This study complies with reference methodology MR004 of the Commission Nationale de l'Informatique et des Libertés. The protocol has received the validation of an ethics committee (Groupe de Réflexion Ethique du CLB, number: 2020-006). The results will be disseminated through conference presentations and peer-reviewed publications.

Trial registration number NCT04717440.

Strengths and limitations of this study

- Semistructured interviews allow for an in-depth analysis of reasons for acceptance and refusal of the mixed management.
- The interest in the reasons for refusal is innovative and rich in clinical implications.
- Combining the data from the interviews with quantifiable data from scales allows for complementary information to be obtained.
- The small sample size does not allow for generalisation and makes this study exploratory.
- A potential challenge for this study may be the difficult recruitment of participants because of their heavy burden of medical care.

INTRODUCTION

Background

When conventional cancer therapies no longer appear to be efficient, patients may be included in early clinical trials (ECTs). Evaluating the toxicity profile of a new molecule is the primary objective of these trials and the first step of drug development. Objective response rate is a secondary endpoint. While it was around 5% in the 1980s, this rate now reaches 20%.¹ Few patients can be included in such protocols as they must meet strict criteria (good performance status, normal biological parameters, etc) and must agree to comply with heavy treatment and examination schedules. Some studies have reported the reasons for accepting or refusing to participate in an early-phase clinical trial. The main reasons for refusal are: lack of understanding of how to access trials decreased physical condition; geographical distance from the health institution; inability to give informed consent;



anxiety–depressive syndrome or opposition within the family circle. Conversely, reasons for acceptance are linked to hope for the cure or stabilisation of the disease, an unrealistic optimistic bias, desire to reassure relatives and contribute to research, absence of other beneficial therapeutic options or the opinion of the referring physician.^{2–7}

For patients taking part in the ECT, the opportunity to be included in a research protocol thus appears to be synonymous with hope of innovative treatments and better management of the disease. After the failure of conventional treatment, patients seem to experience this early-phase trial as a new chance of therapy and frequently the last one.⁸ However, patients do not seem to be aware that this experimental dose-escalation therapy will benefit future patients more than themselves. Some authors have called this belief ‘therapeutic misunderstanding’.^{9–11} Despite their optimism, 35% of patients included in ECTs present depressive symptoms.¹²

The benefits in terms of quality of life linked to inclusion in early palliative care have already been widely demonstrated.^{13–16} Moreover, international recommendations support early palliative care in cancer treatment. As early as 2002, the WHO emphasised the interest of offering early palliative care and its contribution to patients’ quality of life. Several randomised trials have shown the value of early palliative care in symptom control, survival and cost containment.^{14 17 18} Consequently, several international medical societies,¹⁹ as well as the fourth Cancer Plan in France,²⁰ have recommended the introduction of palliative care at an early stage in the treatment process in conjunction with oncological care.¹⁵ For clinicians directly involved in the field, developing a more positive vision of palliative care and integrating it early in oncology treatments may ensure better continuity of care.²¹ However, referral to palliative care still occurs late in the course of the disease and discussing it remains uneasy for both physicians and patients.²²

Palliative care seems to be perceived by patients as a sign that their disease leaves them no way out. The general public primarily associates palliative care with pain relief at the end of life.¹⁹ From the patients’ point of view, being offered palliative care amounts to being told that they will die from the disease they were fighting against until then.^{23 24} However, studies have shown that early palliative care is associated with improved quality of life and decreased depressive and anxiety disorders.^{17 25} While palliative management and inclusion in an early-phase clinical trial may seem antagonistic at first glance, some authors support the idea of a possible synergy in order to improve quality of life, reduce exhaustion symptoms related to side effects and allow patients to complete their treatment protocol.^{26–30} Understanding the issues related to a patient’s decision to accept or refuse early palliative care at the beginning of an early-phase clinical trial thus seems crucial.

Objectives

Faced with these two seemingly opposing perceptions, it is important to better identify the determinants that could impact the patient’s behavioural decision. The main objective of this protocol is to study the reasons for acceptance or refusal of early palliative care in patients entering an ECT.

For all patients, the secondary objectives are:

1. To assess the number and rate (%) of acceptance and/or refusal of early palliative care.
2. To assess the patients’ understanding and perception of the mixed management: what is understood and perceived about being included both in a clinical trial and in palliative care. We will therefore compare the semantic content of the patient–investigator ecological interaction at the time of proposal of trial inclusion and proposal of palliative care (ie, what was said explicitly) with that of post-inclusion interviews (ie, what patients understood, perceived).
3. To describe the patients’ quality of life and anxiety–depression according to their acceptance or rejection of mixed management at inclusion and at the end of the early-phase treatment protocol.
4. To describe the clinical, medical and sociodemographic characteristics of patients according to their acceptance or rejection of the mixed management plan.
5. To describe the aggressiveness of care near the end of life.
6. To describe the overall survival of patients according to their acceptance or rejection of mixed management.
7. To describe how patients who accept mixed management comply with supportive care.

METHOD AND ANALYSIS

Study population

This study will take place in the Léon Bérard Comprehensive Cancer Center in France, which is dedicated to cancer treatment and research. All patients approached for inclusion in an early-phase clinical trial by the multi-disciplinary tumour board will be invited to participate in the study. Participants are therefore included in various early-phase clinical trials. To evaluate the reasons for acceptance or refusal of inclusion in palliative care among patients starting an early-phase clinical trial, two subgroups will be formed. The first group will consist of successive patients who have accepted joint palliative care (n=20) and the second will comprise those who have refused (n=20).

Patients must fulfil all the inclusion criteria: man or woman aged <18 years, participation in an early-phase clinical trial, no prior experience of palliative care, life expectancy ≥16 weeks, no opposition to the collection and processing of data in the present study and affiliation with a social security scheme. They must not present any of the exclusion criteria: difficulty in understanding written French language, emotional or physical vulnerability (eg, determined during the medical consultation

based on the perception of the medical team), guardianship, curatorship or safeguard of justice, current participation in a clinical trial or interventional study related to supportive care.

Sample size

There are no statistical assumptions in this qualitative study about the primary criteria, and therefore no a priori calculation of the sample size. The number of interviews is estimated sufficient when data saturation is reached. Saturation is generally reached after 12 interviews.³¹ Considering there will be 20 interviews for each of the two subgroups (acceptance or refusal), this number provides a sufficient safety margin to ensure the robustness of the analyses. A sample of 40 patients is therefore expected. Quantitative analysis will only be done in a descriptive presentation of the data.

Study assessments

The evaluation criterion for collecting variables related to the main objective is the qualitative evaluation of the reasons for acceptance or refusal of early palliative care in patients included in early-phase clinical trials. The evaluation criteria for the secondary objectives are the following:

1. Numbers and percentages of acceptance or refusal of the ECT for all patients called and having consulted in the early-phase unit.
2. Patients' understanding and perception of mixed management, which will be assessed by comparing the qualitative semantic content of the patient–investigator ecological interaction at the time of the invitation for inclusion in a trial (ie, what was said explicitly) with that of the post-inclusion interviews (ie, what patients understood, perceived).
3. Quality of life, which will be assessed by using the seven-item Functional Assessment of Cancer Therapy-General (FACT-G7),^{32 33} and anxiety–depression will be assessed by using the Hospital Anxiety and Depression Scale (HADS)³⁴ at the inclusion and the end of the ECT.
4. Clinical, medical and sociodemographic characteristics of the patients, which will be evaluated based on:
 - The 10-item screening questionnaire PALLIA 10,³⁵ to identify the ideal time to offer palliative care (10 items) and the prognostic assessment test PRONO-PALL,³⁶ a prognostic tool which helps make ethical and appropriate decisions and could encourage early steps towards a palliative care pathway for the patient and his/her relatives (three items).
 - The Edmonton Symptom Assessment System (ESAS),³⁷ to assess physical symptoms (nine items).
 - Patients' medical and paramedical history, to describe end-of-life aggression criteria (primary cancer location, date of last chemotherapy, transfer to intensive care unit, emergency hospitalisation possibly in a palliative care unit, number/types of consultations including psychologists, psychiatrists,

pain, nutrition, social services, other supportive care, etc).

- Aggressiveness near the end of life: administration of chemotherapy, radiotherapy to achieve tumour control, emergency room admission or intensive care unit hospitalisation during the last month of life.
- Overall patient survival.
- Age, gender, family situation, place of residence, socioeducational level, professional activity, etc.
- For patients having accepted palliative care, palliative care compliance will be defined by the completion of at least 50% of the planned visits.¹⁷ An initial consultation with the palliative care team will serve to define the patient's needs in terms of psychological follow-up or pain management, for example.

Procedures

Patients eligible to enter an ECT will be identified at a multidisciplinary consultation meeting prior to the study. During the first consultation, the investigator will present the ECT to the patient. The investigator will then ask the patient if he/she agrees to have the next consultation audio-recorded and provide the patient with a consent form for the recording of the following consultation. As part of their medical follow-up, all patients who consent to participate in an early-phase clinical trial will be invited to enter the study.

Prior to the second consultation, patients complete the FACT-G7 and HADS questionnaires. These questionnaires will also be completed at the end of the ECT. The second consultation will start with the patient's consent to be recorded. The purpose of this consultation is to plan the treatment and follow-up of an early-phase clinical trial and to propose concomitant palliative care management to the patient. The patient can accept the ECT and decline the early palliative care.

Patients will be included chronologically according to study set-up. They will be divided into two groups depending on their acceptance or refusal of the early palliative care in addition to the ECT. The first group will comprise patients who have accepted palliative care and the second group those who have refused it.

Patients who will not have declined the ECT and accepted to participate in a single interview with a psychology researcher will be met. The goal of this interview is to better understand the reasons for accepting or refusing the combination of early palliative care with the ECT.

To facilitate analysis, the audio-recording of the consultation and the interview will be fully transcribed by an independent service provider and made anonymous according to a pseudonymised identification code.

After the interview, patients who accept palliative care will have a consultation with the palliative care team (physician and nurse). Following this consultation, the team will offer a follow-up tailored to the patient's needs in addition to their own early-phase clinical trial

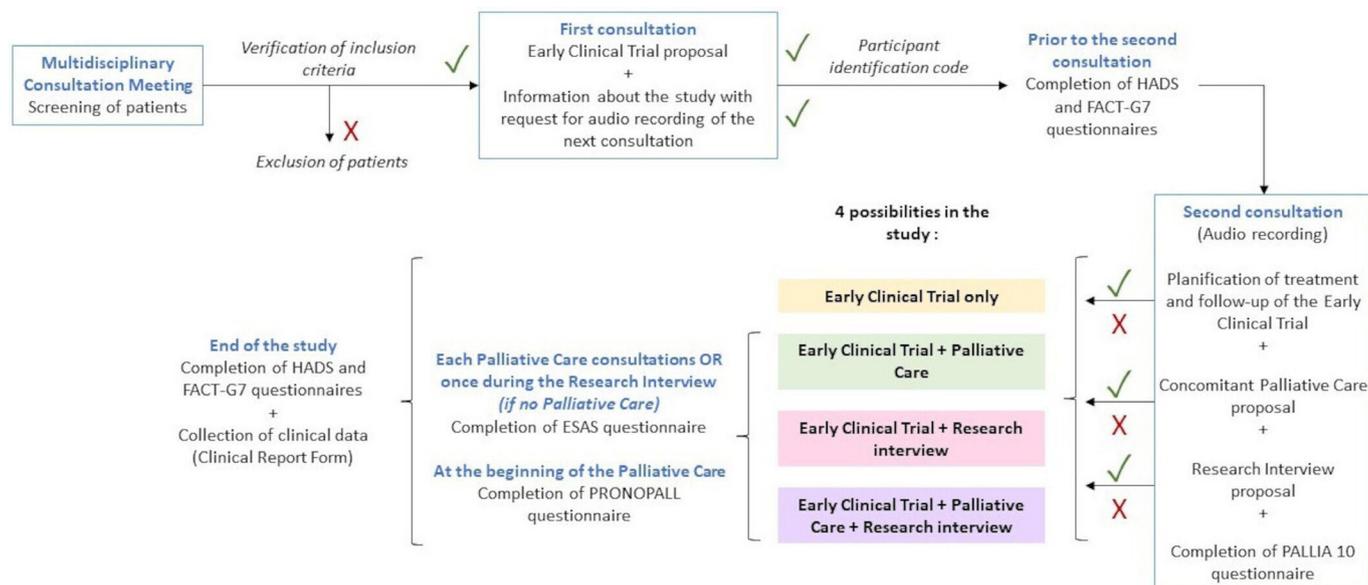


Figure 1 Data collection procedures. FACT-G7, seven-item Functional Assessment of Cancer Therapy-General.

management (psychological support, pain management, nutrition, social support, etc), with at least 1 monthly physical appointment with the physician and the nurse and telephone follow-up with the nurse every month. The palliative care team will follow their usual care activities, there is no special protocol for these patients. Patients who refuse palliative care follow-up will only benefit from the early-phase clinical trial management. [Figure 1](#) shows the steps in the test procedure.

Data analysis

Qualitative analysis

The transcribed consultations and interviews will be analysed by two health psychology researchers using NVivo software, with all the identifying information having been removed. They will be analysed thematically. This analysis will be exploratory following a bottom-up strategy. According to this method, each interview is broken down into thematic segments. The segments are then grouped into themes and subthemes by semantic analogy. It is thus possible to bring out the main concepts of an interview corpus.^{38 39}

Quantitative analysis

A descriptive analysis of the quantitative data will be performed. The quantitative variables will be described by mean, SD, median and range. Nominal and ordinal variables will be described by their number and percentage. Patients' characteristics, including prognostic scores, will be described at inclusion for the whole population and then separately by group (those who accept vs those who refuse). ESAS symptom scores will be calculated according to the authors' recommendations and described at each time point by mean, SD, median and range. The mean change in symptoms will be estimated from baseline and at each follow-up time.

The acceptability of the plan will be assessed by measuring the rate of patients completing at least 80% of the initial plan. Overall survival will be estimated using the Kaplan-Meier method and described using the median and its 95% CI.

Scores of quality of life and anxiety/depression questionnaires will be calculated according to the recommendations of the authors. A descriptive analysis of the scores obtained for the patients who accept the mixed protocol will also be carried out. PRONOPALL and PALLIA 10 will also be used at the two measurement times planned, that is, at inclusion and at the end or exit of their trial. Finally, all these measures will be compared statistically using a non-parametric Mann-Whitney test.

Data management

Interviews will be recorded on a voice recorder. At the end of each interview, the audio file will be transferred to a secure server. The recording of the consultation and the interview will be fully transcribed by an independent company and made anonymous by a pseudonymised identification code. Once transcribed, the original recordings will be destroyed in order to guarantee the anonymity of the participants. Patients will be identified in the study using coded information (patient number for the study, partial date of birth (date and month of birth only), initials), thus allowing data from the different sources of the study (clinical database, records from the consultation and interview) to be compared. A correspondence table will be retained at the investigational site and will be accessible only to the healthcare professionals involved in the patients' care.

Data from the patients' medical file and data from the quality-of-life questionnaires will be reported by trained investigational staff in a secure dedicated database developed by the sponsor (ENNOVclinical software).

Automatic data controls and risk-based monitoring will ensure data consistency.

Patient and public involvement

No patient or public involvement.

ETHICS AND DISSEMINATION

This study complies with reference methodology MR004 of the Commission Nationale de l'Informatique et des Libertés and was registered on 15 June 2020 by the Data Protection Officer of the Centre Léon Bérard on the activity registry of the institution (Ref. R201-004-064). Personal data will be collected and processed in accordance with the laws and regulations in force. The protocol has received the validation of an ethics committee (Groupe de Réflexion Ethique du CLB, number: 2020-006). It was registered on ClinicalTrials.gov. The study started on 05 February 2021 with the first patient being informed about the study. The study will be completed once all the patients have completed their participation in their clinical trial. The study is expected to last until January 2023.

All documents related to the study as well as the study database will be kept by the Léon Bérard Comprehensive Cancer Centre for 2 years after the last publication. They will then be archived (after publication of the results) for a minimum of 15 years, either on the premises of the centre or with a service provider specialised in medical archiving, in accordance with the French decree of 11 August 2008.

A final scientific report of the research project will be written by the principal investigator, including the results and clinical outcomes of the study. Research results will be available to participants in accordance with the terms described in the information documents. The results of this study will be disseminated through conference presentations and in peer-reviewed journals.

Prior to the conduct of research involving human subjects, the investigator must inform the patient of all aspects of the research relevant to his or her decision, in accordance with applicable laws and regulations. This information is provided in writing (information note), made available to the patient, and the patient must be given an appropriate period of time to consider whether or not to object to the research. Non-objection is documented by the investigator in the patient's medical record.

The information notice should be revised as necessary whenever there is a substantial change in the study protocol and/or procedures or when new information becomes available that may affect the patient's willingness to participate. A new information leaflet must then be submitted.

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