Early Palliative Care and Hematological Cancer Patients: a Phase II Study

NCT number: NA

Date: May , 15th, 2018

Research protocol on early palliative care and hematological cancer patients: a phase II study.

Introduction

The most recent World Health Organization (WHO) definition of palliative care advocates that palliative care principles "…should be applied as early as possible in the course of any chronic, ultimately fatal illness." (Sepulveda 2002). The difference with the previous WHO vision was substantial, as the earlier definition recommended Palliative Care to patients not responsive to curative therapy, limiting its role to the last period of life.

Evidence about the effectiveness of an early integration of palliative care has begun to emerge in the last years, primarily for cancer patients. The results of experimental studies (Temel 2010; Zimmermann 2014; Higginson 2014), showed the effectiveness of early integration of palliative in the management of advanced illness, in improving quality of life (Temel 2010; Higginson 2014), reducing consumption of resources (Temel 2010), and possibly increasing survival (Temel 2010; Higginson 2014). These data were also confirmed in Italy (Maltoni 2016, Costantini 2017).

Hematological advanced patients suffer from a very high symptoms burden, psychological, spiritual, social and physical symptoms. They are very similar to oncological advanced patients (Manitta 2011;Le Blanc 2015). Hematologic patients during the last 30 days of their life are more frequently admitted in Hospital setting, emergency departments and high care ward than oncological patients, they received more aggressive treatments and more chemotherapy or biologic active treatments than oncologic patients (Hui 2014)

Looking to WHO's palliative care definition and hematologic patients' symtpoms burden it's simple to imagine that an early access to palliative care service could be the answer, as it was for advanced oncologic patients. The rational of the new vision lied on the recognition that palliative care had the potential to improve quality of life of patients and their family members during the whole trajectory of an incurable disease, through an effective management of psychological and physical symptoms, appropriate relationships, effective communication and support in decision-making.

In addition, even if WHO definition is referred to incurable patients, recent experience on Palliative care and Hematology is also about potentially curative patients. (Roeland 2015, Barbaret 2018).

Nonetheless, access to palliative care in hematologic patients care results totally absent or confined

in the last days of life (Howell 2011; Corbett 2013).There is a resistance by hematologic specialists to address patients to a palliative care service because of the possible misunderstanding between active treatment and palliative care assistance, identified from many professionals as terminal care (Auret K 2003)
A call to a new model of integration between palliative care and hematologic service is strong (Bandieri E 2013); for some authors just from the beginning of an advanced disease (Odejie 2016) and for other authors modelled on the different patients' needs (Manitta 2010, Tuca 2017)

The aim of the study is to pilot a new model of integration for advance hematological cancer between hematological and palliative care. Eligible patients will be at the last active treatment (chemotherapy or immunotherapy) as decided by hematologists.
The primary aim is to evaluate the feasibility, acceptability and efficacy of this novel intervention.
The evaluation procedure will be evaluated for feasibility and applicability
To our knowledge this is the first trial on an integrative model between palliative care and hematology for an advanced hematological population.

Primary aim

To evaluate the feasibility of integrated versus standard involvement of palliative team for hematological advanced patients.

Secondary aims

- ✓ to evaluate the efficacy of this new model on Quality of Life (QoL) until 6 months after the enrollment.
- ✓ to evaluate the impact of the intervention on care pathways (number of chemotherapies in the last 30 days, number of exams, length of stay in Hospital or Hospice, access to emergency department, setting of death and so on)
- ✓ to evaluate the acceptability of the intervention by patients, professionals and caregivers.

Methods

Study design

This is a randomized control trial, phase II, systematic versus on demand palliative care
The eligible patients , after providing consent, will be randomized:

A. Sperimental arm. Patients in this arm will meet with the palliative care team soon after the decision on their last active treatment
B. Standard arm. Patients in this arm will meet palliative care team at the discretion of their hematologist or at their request

The study was defined as a complex intervention according to MRC framework (Campbell 2000; Campbell 2007). It is a mix method phase II study.

Population

The study will enroll 60 patients, both inpatients and outpatients as established in inclusion criteria. Additionally, the study will include 6 caregivers, 6 patients and 6 professionals for the qualitative interviews.

Inclusion Criteria

- Histologically or cytologically confirmed incurable hematological tumor
- Estimated prognosis by the hematologist more than 1 month at least
- Predictive last active treatment (chemotherapy or immunotherapy) as established by hematological equipe.
- 18 years old;
- ECOG ≤ 3;
- Ability to read and respond to questions in Italian;
- Consent to the study

Exclusion criteria

- Existence of other co morbid disease which in the opinion of the investigator prohibits participation in the protocol
- Caregiver's absence

Participants will be recruited from a Hospital Hematology department. Participation in the study will be strictly voluntary. Hematologic physicians and palliative care physicians identify eligible patients during weekly cases' discussion in the Hematological department. A research nurse will give to each eligible patient a description of the study.The referring hematologist will obtain written informed consent prior the randomization. Once a patient has been consented an external researcher will submit the questionnaires before randomization.
Study participants will be randomized from the statistical department in a 1:1 fashion to the integrated or standard palliative care intervention. Participants who are randomized to the integrated arm will meet the palliative care team before starting the last active treatment. Participants randomized to standard palliative care will be evaluated and followed by the palliative care team at the discretion of their treating hematologist or at their request.

Palliative Care intervention

Palliative care intervention is realized by professionals trained nurses and physicians who provide care and support in inpatients and outpatients setting.

This Palliative care service, defined as "Specialist Palliative Care Team" (SPCT), may include, as established by systematic reviews on this topic (Higginson 2003; Gomes 2009):

a. two or more professionals fully involved in SPCT;
b. at least one of them with a specialized degree in palliative;
c. palliative care for both inpatient and outpatient setting

In this study, the palliative care intervention will guarantee by Palliative Care Unit. Two physicians and two nurses constitute the Unit. Psycho oncologic unit can be involved for more complex clinical cases.
The initial assessment will occur in the outpatient clinic or in the ward as consult. Anyway, it will be achieved before the starting of the last active treatment. Once patients are discharged from the hospital they will be followed outpatients pursuant to the study guidelines.
The SPCT will follow each patient on regular basis in conjunction with his or her primary hematologist. Professionals or patients and their families will arrange additional visit at their discretion.
Palliative care team and treating hematologists will discuss active patients issue to assure a team approach to the patient's care. They participate to the weekly cases' discussion in Hematology department. In case of urgent and important issue they discuss each patient by telephone or planning clinical encounter together.

Palliative care service will follow the outpatients until is possible. The assistance will be interrupted for patients deny, death or any causes could make impossible the ambulatory assistance.

Standard palliative care intervention

Patients randomized to the standard palliative care arm will be seen by the SPCT at the request of their hematologist at any time. The care will not be standardized but planned on patients 'needs.

Evaluation pattern and instruments
The study considers a qualitative and a quantitative evaluation.

Quantitative evaluation

Primary endpoint

Feasibility will be collected on the % of randomized patients who will follow the palliative care program during the 3 months after the enrollment

Secondary Endpoints

1. The efficacy on QoL during the follows 6 months will be assessed by

- POS (Palliative Care Outcomes Scale)
- ESAS (Edmonton Symptom Assessment System)
- HADS (Hospital Anxiety and Depression Scale)
- ECOG (Eastern Cooperative Oncology Group)

Palliative Care Outcome Scale (POS; Hearn & Higginson, 1999): (POS) is a widely used, validated also in Italy (Costantini et al 2016), brief outcome measure, used in in-patient, community and outpatient settings among patients with advanced illnesses. The original English version of the POS comprises 10 items, including physical and psychological symptoms, spiritual and emotional dimensions, communication with patients and families and practical concerns related to stage of disease. The POS also includes an open optional question to list the main concerns. Each of the 10 items is scored with a Likert scale ranging from 0 to 4.
The ESAS (ESAS; Bruera et al., 1991) instrument asks respondents to rate the severity of 10 common symptoms (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well-being) during the previous 24 hours. This questionnaire has been found to be valid and reliable in cancer populations.

Eastern Cooperative Oncology Group (ECOG Performance Status; Oken et al., 1982): the ECOG performance status is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis

- grade 0: fully active, able to carry on all pre-disease performance without restriction
- grade 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
- grade 2: ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours
- grade 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- grade 4: completely disabled, cannot carry on any self-care, totally confined to bed or chair
- grade 5: dead

The HADS (HAD R.P. Snaith and A.S. Zigmond,1983) is a self-assessment 14-item questionnaire which has been well tested in cancer patients. It has two 7-item subscales assessing depression and anxiety in the preceding week. The scale is considered appropriate for cancer patients because of the lack of items regarding somatic symptoms, which can confound the identification of psychiatric issues. The format consists of four responses (0-3) that quantify the degree to which a particular emotion is experienced by the patient. The score on each subscale ranges from 0 to 21 and a score

of greater than 11 is considered to be consistent with definitive depression or anxiety. A score of less than 7 is normal and a score of 8–10 is considered borderline for depression and anxiety

2. the efficacy on health processes and procedures will be collected by indicators recoverable in electronic data base (see session below)

The quantitative assessment

We consecutively register all eligible patients (and reasons for ineligibility) both from Hematological department, patients who were asked to participate to the study (and reasons for not), patients who accepted to participate (and reasons for not).

We register all visits with the patients (outpatient visits and consultation during hospital admissions) and with family members. We collect from medical records information about hospital and emergency admissions, anticancer chemotherapies (drugs and date of administration), referral to community PC services (domiciliary PC teams and inpatient hospices), date and place of death, overall survival.

Tree questionnaires will be proposed to the patients for self-assessment by 2 trained researches after the consent (T0), at 4 weeks (± 7 days) after t0 (t1), at 8 weeks (± 7 days) after t0 (t2), at 12 weeks (± 7 days) after t0 (t3), at 16 weeks (± 7 days) after t0 (t4), at 20 weeks (± 7 days) after t0 (t5) and at 24 weeks (± 7 days) after t0 (t6)

Once the questionnaires will be submitted in Hospital and then depending on patients ‘preferences for the following evaluations (at time 1 (t1) to time 6 (t6).

The Quantitative assessment (questionnaires and information from medical records) will be collected for both the arms, sperimental and standard one

Statistical methods

The feasibility of the early integrated PC intervention was assessed estimating the proportion of

hematologic patients who accepted to participate in the intervention and attended the first PC visit. We plan to recruit 60 study participants. The feasibility will be achieved if >50% of patients remain in the program in the next 3 months from the enrollment

It will be possible to assess the feasibility of the experimental intervention assuming 5% as level of significativity and 80% as statistical power on the basis of the subsequent hypotheses:

1) planned statistical test: chi-squares with 1 degree of freedom;
2) type of comparison: 2 tailed;
3) p-value calculation mode: exact (because the small sample size);
4) alternative hypothesis: 75%;
5) allocation ratio: 1:1.

(Power analysis was performed using nQueryAdvisor, sheet POT0x, version 7.0).

To reach the primary objective, the statistical test as cited at point 1 will be used according to specification better detailed at point 2 and 3; about the tested percentage, the exact two-sided 95% confidence interval will be calculated according to the Clopper-Pearson approach.

About the secondary objectives, each score related to the PRO tools (POS, ESAS, HADS, ECOG) will be assessed in terms of temporal evolution and differences between the two arms using GEE models. Furthermore, within each arm and for each observational time, it will be calculated (for each score):

- the mean with its 95% two-side confidence interval (assuming asymptotic normality for the related estimator);
- common descriptive statistics (minimum, maximum, main percentiles, standard deviation).

The same approach will be followed for each change measure vs baseline, where such kind of change has to be intended in terms of difference between the score value at the time of interest and the related value at baseline.

If it will be deemed useful, such change measures can be depicted in relative way (eg, as percentage vs the related baseline value).

Statistical analyses will be performed by staff of Clinical Trials and Statistics Unit. To this aim, SAS System or R will be used according availability and version in use.

Qualitative assessment

Consent to the qualitative assessment will be requested to a consecutive series of six patients and six family members (from patient's others than previously selected) who would attend at least three visits in the PC outpatient clinic. A qualitative assessment will also be proposed to a sample of six physicians involved in the care of patients recruited in this study, selected among those who will follow the highest number of patients.

Information will be gathered through three individual semi-structured interviews exploring the experience of the different 'actors' of the intervention, i.e. the receivers (patients and family members) and the physicians involved in the early integrated palliative care.

Interviews address to patients and family members focused on perceived benefits and concerns of the early PC intervention, with reference to the main domains which informed its structure. Interview address to physicians focused on exploring strengths and weaknesses of the intervention with reference to both the respondents' view on patients' and family caregivers' experience, and their own role (including specific tasks required to them) within the study.

A member of the research team with expertise in qualitative evaluation in palliative care develop the topic guide of the interviews. If the identified participant agrees with the evaluation, an interviewer contact him/her. Anonymity and non-traceability criteria will be duly presented to all interviewees. Explicit permission is requested for the interview to be audio-recorded. Interviewers are two nurses with expertise in palliative care, with basic knowledge of the intervention but not involved in its implementation.

Data analysis

Tape recordings of the interviews are transcribed verbatim, and then analyzed using thematic

analysis to explore the content and context of responses (Payne et al 2007).

In the first step, one researcher develops coding schemes covering themes congruent with the structure of the interview topic guides. Then two researchers independently analyze the transcripts and categorized all segments of the text potentially relevant to the interview topics. Throughout an iterative process, they inductively identify a number of subthemes. In the second step, the two researchers compare the categorizations, and reconsider and discuss any differences in interpretation in order to reach an agreement, and to develop a unique preliminary categorization. Finally, a third researcher revise both the transcripts and the preliminary categorization, regroup and rename some themes and subthemes with the objective of describing them through highlighting commonalities and differences between the perspectives of the three 'actors' enquired. This revision will be discussed and emended with the other researchers involved in the qualitative analysis.

Ethics

The study protocol has been approved by the Ethics Committee. No financial compensation will be provided to the participants in the study. In accordance with good clinical practice patients will be informed about participation in the study and its implications. Written consents will be obtained

Conclusions

This pilot study will evaluate the feasibility of an integration between hematology and palliative care teams as routine practice. This study also aims to collect the perceived strengths and barriers of integration from professionals, patients and careers. This study will complement previous studies on cancer patients focusing on hematological patients with a short life expectation and a various burden of symptoms, physical, psychological, social and spiritual ones.

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