Rationale and study design: A randomized controlled trial of early palliative care in newly diagnosed cancer patients in Addis Ababa, Ethiopia

Eleanor Reid a, *, Ephrem Abatham b, Jilcha Diribi d, Yoseph Mamo b, Peter Hall c, Marie Fallon c, Tigineh Wondemagegnhu d, Liz Grant e

a Yale University School of Medicine, New Haven, USA
b Hospice Ethiopia, Addis Ababa, Ethiopia
c Cancer Research UK Edinburgh Centre, University of Edinburgh, Edinburgh, UK
d Addis Ababa University College of Health Sciences, Addis Ababa, Ethiopia
e University of Edinburgh Global Health Academy, Edinburgh, UK

A R T I C L E   I N F O

Keywords:
Palliative care
Cost consequence analysis
Low income country

A B S T R A C T

Patient-reported outcomes and economic aspects of Palliative Care (PC) provision in low-income countries (LIC) are under-studied. Demonstrating the economic value of PC is key to sustainability and guiding health care policy. Our preliminary data in Ethiopia demonstrated a widespread need for PC, poor access to it, and high out of pocket payments (OOP). We suspect that in this and other LIC, PC may function not only to reduce suffering but also as a poverty reduction strategy.

We are conducting a randomized controlled trial of standard Oncology care versus standard Oncology care plus PC in newly diagnosed cancer patients in Addis Ababa. Ninety-seven adults presenting to Oncology Clinic will be randomized in a 1:1 ratio. Subjects receiving PC will meet with a PC provider at time of enrollment and at follow up visits in their homes. All subjects will be assessed via questionnaire at enrollment and follow-up Oncology visits at 8 ± 4 and 12 ± 4 weeks. A cost-consequence analysis will be performed, to include: patient-reported OOP and healthcare utilization, the latter to be assessed through chart adjudication. Outcomes will include change in African Palliative Care Association Palliative Outcome Score, changes in OOP and healthcare utilization.

We hypothesize that the cost of home-based PC will be offset by improvements in patient-reported outcomes, decreased OOP and healthcare utilization, rendering PC cost-effective in this LIC. These findings may lead to widespread dissemination of an effective, sustainable and cost-saving public PC delivery strategy that would improve the quality of life and death for millions of people.

Trial registration: Clinicaltrials.gov NCT03712436.

1. Introduction

With the rise in non-communicable diseases (NCD), an epidemiological transition is underway: globally, people are living longer with incurable disease [1]. As a result, there is a great need to expand health care delivery for all stages of chronic illness, including palliative care. Of the 61 million people globally in need of palliative care, just 14% receive it, largely in high-income countries [2–4]. Within fragile health systems that lack palliative care, incurable illness is often marked by pain and suffering, as well as devastating costs of seeking medical care [5]. Universal Health Coverage calls for quality healthcare for all, from preventative to palliative, without financial burden, yet globally, millions of people are impoverished by the costs of seeking medical care [6–8].

Out of pocket payments (OOP) refer to payments made directly by individuals to healthcare providers, at the point of service. In settings where healthcare providers are inadequately paid, OOPs provide a major source of revenue, while simultaneously absorbing the financial

* Corresponding author. Yale University School of Medicine, 464 Congress, Ave, Suite 260, New Haven, CT, 06519, USA.
E-mail address: Eleanor.reid@yale.edu (E. Reid).

https://doi.org/10.1016/j.conctc.2020.100564
Received 19 December 2019; Received in revised form 20 March 2020; Accepted 28 March 2020
Available online 6 April 2020
2451-8654/© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license
resources of a patient, thus increasing the incidence of catastrophic health expenditures (CHE). CHE is defined as out-of-pocket spending for healthcare that exceeds a certain percentage of household income, with the consequence that households suffer the burden of disease [9].

In countries that rely on OOPs to finance their healthcare system, the financial burden of medical care is borne by patients and families, often at the expense of essentials such as food and children’s education. High OOP also may discourage patients from seeking medical care, or be a factor in delaying the seeking of care [10]. In Africa, the risk of CHE is increased in the following vulnerable groups: low socioeconomic status, rural residence, not having health insurance, long inpatient days and having a chronic disease [11,12].

We previously reported the results of a palliative care needs assessment in Ethiopia, which demonstrated a great need for palliative care provision, particularly in the Oncology population, and the tremendous costs of illness, largely in the form of OOP, that are absorbed by patients with incurable disease and their families, often with little knowledge of prognosis. In order to cope, children were pulled from school as fees became unaffordable, and major assets were sold, including livestock, land and wedding gold [13].

Other results included high pain scores coupled with inadequate access to analgesic medications and high OOPs for incurable illness, often with little to no knowledge of prognosis. [11] We concluded that the need to formally implement public palliative care interventions is an urgent priority, and hypothesized that palliative care may function as a poverty reduction strategy in this and other low income countries (LIC) through a decrease in OOP and healthcare utilization [14].

We recently published a systematic review of the cost-effectiveness of global palliative care, the results of which highlighted the need for more, and robust, cost-effectiveness analyses in LIC [15]. Demonstrating the economic value of palliative care in LIC is key to sustainability and crucial for guiding health care policy [16,17].

2. Methods and study design

2.1. Overview

There are two overarching specific aims in this project. The first is to study the effect of initiation of palliative care on patient-reported palliative outcome measures as assessed by the African Palliative Care Association Palliative Outcome Scale (APCA POS) [18] and Needs Near End of Life Screening Tool (NEST 13). [19] We expect improved quality of life and decreased symptom burden, as measured by a significant decrease in both scores in those patients receiving palliative care.

The second aim is to perform a Cost Consequence Analysis (CCA), a type of economic analysis that looks at disaggregated costs and consequences and is thought to be a specifically useful tool for assessing complex interventions with multiple effects, and interventions with a variety of non-health benefits, such as palliative care [20,21]. The CCA will evaluate the following: (1) the cost of delivery of home-based palliative care over the study duration, (2) patient-reported OOP for medical care, (3) hospital-generated costs and healthcare utilization in those patients receiving palliative care, (4) patient-reported outcomes including change in APCA POS and NEST scores, and (5) survival.

A societal perspective will be considered, and comprised of three key perspectives: the patient and family as fully one third of medical expenses in Ethiopia are OOP borne by the patient and family [22,23], Hospice Ethiopia as the deliverer of Palliative Care, and the government, as they health system payer (see Fig. 1: Study Flow).

2.2. Study population

A sample size of 47 per group is needed to provide 80% power to detect a difference of 3 at week 8 on the APCA POS score at a 2-sided significance level of 0.05 and attrition of 25%, assuming standard de-
2.2. Subjects and sampling

Patients with newly diagnosed cancer who are ambulatory and able to respond verbally to questions are eligible for inclusion. Patients with diagnoses made more than 4 weeks ago, who are non-ambulatory, or are already receiving palliative care, are ineligible to participate in the study. All eligible patients will be approached for enrollment. No other recruitment will be done. Subjects will be randomized via a web randomization tool in a 1:1 ratio to one of the two study arms. All subjects will provide written informed consent. All subjects will receive standard oncologic care throughout the study period unless they or their family decide that standard oncologic care no longer aligns with their goals of care, in which case they will be withdrawn from the study however offered ongoing Palliative Care through Hospice Ethiopia, should they desire it.

2.3. Intervention and comparator

Subjects randomized to early palliative care will meet with a Palliative Care provider at time of enrollment and at follow up visits in their homes, as frequently as deemed indicated by Hospice Ethiopia staff, and according to Hospice Ethiopia guidelines for the practice of Palliative Care in this setting. Palliative care providers are Ethiopian physicians and nurses trained in palliative care practices. All subjects in both study arms will be assessed via questionnaire at enrollment and at follow up visits in Oncology clinic. (Fig. 2, Supplementary file). No data will be collected during home hospice visits. Follow-up will occur at 8 weeks (or at an outpatient clinic visit within 4 weeks before or after this time point) and at three months.

2.4. Outcomes

To evaluate the impact of initiation of Palliative Care in this population, we will measure the proportion of subjects in both study arms with improved quality of life, as measured by a decrease in APCA POS or NEST 13 scores (Table 1: Quality of Life Outcomes). We will also compare OOP for medical care, healthcare utilization and survival.

2.5. OOP and healthcare utilization

To estimate healthcare utilization, hospital charts of subjects in both study arms will be adjudicated at study end for costs generated by the clinic and hospital (Table 2). Chart adjudication will be performed by native Amharic speakers with a degree of Registered Nurse or Medical Doctor, and experience working in an Oncology population. Economic results will be reported in 2019 USD.

2.6. Intervention costs

The cost of delivering home-based palliative care is estimated at 265 Ethiopian birr/visit (9.25 USD), which includes the time of the healthcare worker, gas, and medicines. The estimate does not include overhead costs of running Hospice Ethiopia (building rental, janitorial fees, vehicle) as this is already in place.

2.7. Ancillary study: novel biomarker

The neutrophil to lymphocyte ratio (NLR) is being evaluated as a predictor of longevity and response to chemotherapeutics. This simple calculation, available from a widely available and basic blood test that is already drawn at the time of presentation to Oncology clinic, may provide powerful information to help guide Oncologists in their discussions with patients about the risks, benefits and costs of pursuing treatment. It is particularly important in resource limited settings, and in settings with poor health infrastructure where patients and families absorb the costs of illness. Thus far, it has only been studied in northern populations [24,25]. The NLR will be calculated at study end, during the hospital chart adjudication.

3. Discussion

We are publishing our study protocol in order to increase the transparency of the economic evaluation within our clinical trial, and to provide a template for conducting a CCA of palliative care in a low resource setting. The protocol follows international guidelines for economic evaluations [26,27]. Economic evaluations from high income countries have shown that palliative care is cost-effective [28-34]. A dearth of similar analyses in low resource settings has produced a gap in hard health economic data on palliative care delivery in low income settings [13]. Our aim in providing this template is to encourage other CCA of palliative care in similar settings, thus generating the data to support the funding of widespread, public palliative care services in low resource settings.

This manuscript describes the protocol for an economic evaluation of a randomized controlled trial of Palliative Care in newly diagnosed cancer patients in Addis Ababa, Ethiopia. There are some notable strengths of this study. First, the study design is a randomized controlled trial of early palliative care in a low resource setting. As such, it is the first of its kind on the continent of Africa and is responding to

---

Subject Process

Black Lion Outpatient Oncology Clinic
- Patient arrives for baseline or follow-up Oncology appointment

Registration/Charts Desk
- Patient picks up his/her chart and walks to be called

Laboratory
- Patient may be asked to go to outpatient laboratory for bloodwork and then return to clinic

Case Report Form
- To be completed in private clinic room by Research Staff (phlebotomists) during visit at baseline and follow up

Outpatient Dispensary
- Patient collects any prescriptions at OPD prior to going home

Fig. 2. Subject process.
Table 1
Quality of life outcomes.

| Outcome                                      | Source | Time of collection |
|----------------------------------------------|--------|--------------------|
| APCA POS (scale of 0–5)                     | CRF    | CRF                |
| Pain                                         | CRF    | Baseline, follow-up visits |
| Other symptoms                               | CRF    | Baseline, follow-up visits |
| Worry                                        | CRF    | Baseline, follow-up visits |
| Able to share feelings                       | CRF    | Baseline, follow-up visits |
| Life feels worthwhile                        | CRF    | Baseline, follow-up visits |
| Sense of peace                               | CRF    | Baseline, follow-up visits |
| Able to plan for future                      | CRF    | Baseline, follow-up visits |
| Information given to family                  | CRF    | Baseline, follow-up visits |
| Family able to care for patient              | CRF    | Baseline, follow-up visits |
| Family worry                                 | CRF    | Baseline, follow-up visits |
| NEST 13 (scale 0–10)                         | CRF    | CRF                |
| Financial hardship                           | CRF    | Baseline, follow-up visits |
| Trouble accessing care                       | CRF    | Baseline, follow-up visits |
| Help needed with ADLs                        | CRF    | Baseline, follow-up visits |
| Illness seems senseless/meaningless          | CRF    | Baseline, follow-up visits |
| Suffering from physical symptoms             | CRF    | Baseline, follow-up visits |
| Confusion/anxiety/depression                 | CRF    | Baseline, follow-up visits |
| Have someone to confide in                   | CRF    | Baseline, follow-up visits |
| Religion/spirituality contribute to purpose  | CRF    | Baseline, follow-up visits |
| Settled relationships with family/friends    | CRF    | Baseline, follow-up visits |
| Special sense of purpose                     | CRF    | Baseline, follow-up visits |
| Worry about the costs of care                | CRF    | Baseline, follow-up visits |
| Money spent in last month on medical care    | CRF    | Baseline, follow-up visits |
| Caretaker lost wages                         | CRF    | Baseline, follow-up visits |
| Sale of personal belongings to pay for medical care? | CRF | Baseline, follow-up visits |

Table 2
Cost measures.

| Type of cost                                      | Source | Timing of collection | Units    |
|---------------------------------------------------|--------|----------------------|----------|
| Patient-reported Costs                             | Out of Pocket payments for all medical costs in the last month | Baseline and follow-up visits | Ethiopian birr |
| Worried about the costs of care                   | CRF    | Baseline and follow-up visits | Y/N |
| Time caretaker has taken off of work              | CRF    | Baseline and follow-up visits | Ethiopian birr |
| Lost wages                                        | CRF    | Baseline and follow-up visits | Ethiopian birr |
| Sale of personal items to cover medical costs     | CRF    | Baseline and follow-up visits | Y/N and free text |
| Hospital-generated costs                          | Metastatic work up | Hospital chart adjudication | Study end | Ethiopian birr |
| Diagnostic imaging (CT/Xray)                      | Hospital chart adjudication | Study end | Ethiopian birr |
| Chemotherapeutics                                 | Hospital chart adjudication | Study end | Ethiopian birr |
| Non-opioid pain medications                       | Hospital chart adjudication | Study end | Ethiopian birr |
| Opioid analgesia                                  | Hospital chart adjudication | Study end | Ethiopian birr |
| Medical procedures                                | Hospital chart adjudication | Study end | Ethiopian birr |
| Hospitalizations                                  | Hospital chart adjudication | Study end | Ethiopian birr |

study. We have tried to mitigate this with a randomized controlled trial study design as our Oncologist is blinded to study group, he is unaware which of his patients are also receiving palliative care and is thus offering the same care to patients in both study arms. This should minimize bias between groups. The study is not designed to control or account for outcome differences in particular cancers at certain stages.

We included patients only from Addis Ababa in this study, for ease of follow up. As Tikur Anbessa is a tertiary hospital, patients travel great distances for care, and then often return to their homes, which would have made follow up near-impossible. Another limitation is the relatively short follow-up period. The main risk of this short follow up is that our study will not detect a significant effect of palliative care due to the short follow up period. The reason this follow up window was selected is due to the very late presentations for cancer and thus short survival window in this population, and needing to find equipoise between minimizing loss to follow up which would likely occur with a longer follow up window, with following patients long enough to detect a difference between groups. There is a risk that the short follow up period may minimize differences between groups or incorrectly fail to show a difference (false negative result). These aspects of our study may introduce some selection bias into our study and do limit the applicability to other populations.

The reliance on patient-reported OOP for medical costs may impact the validity of study results. It also may be difficult in a subsistence economy for subjects to generate number-based responses. However, we have used faces when possible (for patient-reported outcomes) also asked about the sale of major assets, which in our previ-
ous work in this setting, proved to be an effective way of ascertaining the degree of financial stress placed on a family during a time of illness.

In conclusion, we hypothesize that the cost of delivery of home-based palliative care will be offset by improvements in patient-reported outcomes, a decrease in OOP and healthcare utilization, thus rendering the delivery of palliative care cost-effective in this low-resource setting. These ground-breaking results will be highly relevant to patients and families struggling with both poverty and high medical costs, and to healthcare workers and policy makers working to improve palliative care delivery for millions of people with incurable disease.

Ethics

Institutional Review Boards at Yale University School of Medicine and Tikur Anbessa College of Health Sciences approved the study. All patients provided written informed consent prior to participating in this study.

Funding

This study is funded by Yale University School of Medicine, Department of Emergency Medicine, through a New Investigator mechanism awarded to Dr. Reid.

Declaration of competing interest

All authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.concct.2020.100564.

References

[1] Collaborators, et al., Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet 388 (10053) (2016 Oct 8) 1603–q158.
[2] World Health Organization, Palliative care fact sheets Available at: Accessed 11 April 2019 http://www.who.int/media-centre/factsheets/fs402/en/.
[3] F.M. Knaul, P.E. Farmer, E. Krakauer, et al., Alleviating the access abyss in palliative care and pain relief—an imperative of universal health coverage: the Lancet Commission report, Lancet (2017) (published online Oct 11.), https://doi.org/10.1016/S0140-6736(17)32513-8.
[4] World Health Organization, Global atlas of palliative care at the end of life Available at: Downloaded 1/28/2016 http://www.who.int/cancer/publications/palliative-care-atlas/en/.
[5] Krakauer E et al Palliative care and pain control. In: jamison, dean T.; gelband, helen; horton, susan; jha, prabhat; laminarayn, ramnam; mock, charles N.; nugent, rachel. 2017. Disease Control Priorities, third ed.; : Volume 9. Improving Health and Reducing Poverty. Washington, DC: World Bank. © World Bank. https://openknowledge.worldbank.org/handle/10986/28877 License: CC BY 3.0 IGO.
[6] WHO, Making Fair Choices on the Path to Universal Health Coverage. Final Report of the WHO Consultative Group on Equity and Universal Health Coverage, WHO, 2013.
[7] World Health Organization, Cost-effectiveness and strategic planning (WHO-CHOICE), Accessed 11 April 2019 http://www.who.int/topics/health_economics/en/.
[8] T. Boerma, P. Ezenoju, D. Evans, et al., Monitoring progress towards universal health coverage at country and global levels, PLoS Med. 11 (2014) e1001731.
[9] Y. Li, Q. Wu, L. Xu, Factors affecting catastrophic health expenditure and impoverishment from medical expenses in China: policy implications of universal health insurance, Bull. World Health Organ. 90 (2012) 664–671, https://doi.org/10.2471/BLT.12.102178.
[10] World Health Organization, WHO estimates cost of reaching global health targets by 2030, Accessed 11 April 2019 https://www.who.int/en/news-room/detail/17-07-2017-who-estimates-cost-of-reaching-global-health-targets-by-2030.
[11] M.D. Hoffman, K.D. Rao, A. Pichon-Riviere, et al., A cross-sectional study of the microeconomic impact of cardiovascular disease hospitalization in four low- and middle-income countries, PloS One 6 (2011) e20821.
[12] K. Xu, D.B. Evans, K. Kawabata, et al., Household catastrophic health expenditure: a multicountry analysis, Lancet 362 (2003) 111–117.
[13] E. Reid, N. Ayers, E. Gudina, D. Wondimamegegny, Y. Mamo, Caring for life-limiting illness in Ethiopia: a mixed-methods assessment of outpatient palliative care needs, J. Palliat. Med. (2018 Feb 9), http://doi.org/10.1089/jpm.2017.0419.
[14] R.E. Anderson, L. Grant, What is the value of palliative care provision in low-resource settings?, BMJ Global Health 2 (2017) e001393, https://doi.org/10.1136/bmjgh-2016-000139.
[15] E. Reid, O. Kovalenko, K. Juhanyik, S. Brown, L. Grant, Is palliative care cost-effective in low-income and middle-income countries? A mixed-methods systematic review, British Medical Journal Supportive and Palliative Care (2018) 1–10, http://doi.org/10.1136/bmjpsp-2018-000499.
[16] S. Smith, R. Brick, S. O’Hara, C. Normand, Evidence on the cost and cost-effectiveness of palliative care: a literature review, Palliat. Med. 28 (2) (2014) 130–150.
[17] R.E. Anderson, L. Grant, What is the value of palliative care provision in low-resource settings?, BMJ Global Health 2 (2017) e001393, https://doi.org/10.1136/bmjgh-2016-000139.
[18] R. Harding, et al., Validation of a core outcome measure for palliative care in Africa: the APCA african palliative outcome Scale, Health Qual. Life Outcome 8 (2010 Jan 25) 10.
[19] L.L. Emanuel, H.R. Alpert, E.E. Emanuel, Concise screening questions for clinical assessments of terminal care: the needs near the end of life care screening tool, J. Palliat. Med. 4 (2001) 465–474.
[20] M. Drummond, M. Sculpher, G. Torrance, B. O’Brien, G. Stoddart, Methods for the Economic Evaluation of Health Care Programmes, Oxford, Oxford University Press, 2005.
[21] J. Braizer, J. Ratcliffe, J. Salomon, A. Tushiya, Measuring and Valuing Health Benefits for Economic Evaluation, Oxford, Oxford University Press, 2007.
[22] World Bank, Ethiopia country profile, 2016 Accessed 11 April 2019 http://www.worldbank.org/en/country/ethiopia.
[23] 2010/2011 Federal Democratic Republic of Ethiopia MoH. Ethiopia’s Fifth National Health Accounts, Addis Ababa Ethiopia, 2014.
[24] Go, et al., Sarcopenia and inflammation are independent predictors of survival in male patients newly diagnosed with small cell lung cancer, Support. Care Canc. 24 (2016) 2075–2084.
[25] T. Kurita, M. Yamamoto, T. Nagano, D. Hazama, R. Sekiya, M. Katsurada, et al., The timeseries behavior of neutrophil-to-lymphocyte ratio is useful as a predictive marker in non-small cell lung cancer, PloS One 13 (2) (2018) e0193018, https://doi.org/10.1371/journal.pone.0193018.
[26] S.D. Ramsey, R.J. Willke, H. Glick, S.D. Reed, F. Augustovski, B. Jonson, A. Briggs, S.D. Sullivan, Cost-effectiveness analysis alongside clinical trials II an ISPOR good research practices task force report, Value Health 18 (2015) 161–172.
[27] F. Godlee, Publishing study protocols: making them visible will improve registration, reportiing and recruitment, BMC News Views 2 (2001) 4.
[28] P. May, C. Normand, J.B. Cassel, et al., Economics of palliative care for hospitalized adults with serious illness: a meta-analysis, JAMA Intern Med 178 (2018) 820–829.
[29] A.S. Kelley, P. Deb, Q. Du, et al., Hospice enrollment saves money for Medicare and improves care quality across a number of different lengths-of-stay, Health Aff. 32 (2013) 552–561.
[30] Z. Obemeyer, M. Makar, S. Abujaber, et al., Association between the medicare hospice benefit and health care utilization and costs for patients with poor-prognosis cancer, J. Am. Med. Assoc. 312 (2014) 1888–1896.
[31] T.J. Smith, J.B. Cassel, Cost and non-clinical outcomes of palliative care, J. Pain Symptom Manag. 38 (2009) 32–44.
[32] B. Pyenson, S. Connor, K. Fitch, et al., Medicare cost in matched hospice and non-hospice cohorts, J. Pain Symptom Manag. 28 (2004) 200–210.
[33] S. Felder, M. Meier, H. Schmitt, Health care expenditure in the last months of life, J. Health Econ. 19 (2000) 679–695.
[34] C. Zimmermann, R. Riechelmann, M. Krzyzanowska, et al., Effectiveness of specialized palliative care: a systematic review, J. Am. Med. Assoc. 299 (2008) 1698–1706.
[35] S. Ramsey, R. Willke, A. Briggs, R. Brown, M. Buxton, A. Chawla, J. Cook, H. Glick, B. Liljas, D. Petitt, et al., Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA task force report, Value Health 8 (5) (2005) 521–533.
[36] A.P. O’Sullivan, D. Thompson, M.F. Drummond, Collection of health-economic data alongside clinical trials: is there a future for piggyback evaluations?, Value Health 11 (1) (2008) 67–79.