PERGAMON

European Journal of Cancer 37 (2001) S153–S159

European Journal of Cancer

www.ejconline.com

Palliative care research

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Received 2 October 2000; received in revised form 2 May 2001; accepted 17 July 2001

Abstract

Most of the research in palliative medicine is of a descriptive nature. Clinical practice is based upon clinical experience rather than upon research. The level of appropriate research reduces the chance for improvement of palliative care. Ethical and methodological obstacles seem to be prominent in palliative care research. The Declaration of Helsinki is generally accepted as an ethical code of practice for clinical research and it also applies to palliative care. In order to obtain reliable data, standardisation of data collection is needed. Improvement of quality of life is the primary endpoint in most studies in palliative care. The existing validated quality of life instruments such as the European Organization for Research and Treatment of Cancer (EORTC) quality of life (QLQ)-C30 can be used until the patient is too sick to complete the questionnaire. New approaches are needed and must be developed for the dying patients. Palliative care research needs proper funding; specific programmes supporting research on a European level are needed. The European Association for Palliative Care (EAPC) is capable of conducting and coordinating collaborative research in palliative care on a European level.

Keywords: Palliative care; Patient management; Terminal disease; Quality of life

1. Introduction

The World Health Organization (WHO) has defined palliative care as follows: "...the active, total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families. Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with anti-cancer treatment" [1].

Palliative care comprises care for patients who can not be cured. It can be defined as a comprehensive approach, which should include optimal medical diagnostic work-up, use of the best medical treatment possible, excellent nursing care, psychosocial and spiritual support. Additionally, it ought to be family focused. In the beginning of the hospice movement, emphasis was placed on the last days or weeks of a patient's life. The focus has been broadened during the last few decades, to include patients earlier in the trajectory of a terminal disease (Table 1). In order to improve patient care, programmes need to be created, and symptom control, rehabilitation and bereavement services need to be enhanced.

In general, the goal in medicine is to recommend treatments based upon research (i.e. the medicine should be evidence-based). The same applies for palliative medicine. Clinical and organisational challenges will depend upon cultural and geographical factors, probably more so for end-of-life care than for medicine in general. In several European countries, oral morphine is not available for use in routine clinical practice and, if available, restrictions on the prescription rules are substantial. Another challenge is related to the costs of the 'new' slow-release opioids, given either as tablets or applied transdermally. Therefore, an appropriate strategy is to still recommend immediate-release morphine as opioid of choice in several European countries. Organisations such as WHO and the European Association for Palliative Care (EAPC) should work colla-

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0959-8049/01/$ - see front matter
PII: S0959-8049(01)00260-X

Table 1
Some target areas for palliative care delivery and research

Areas of concern			
Patient population	What are the key elements to define the population?	Indicators of survival during end-of-life care	Integration/definition of palliative medicine into the healthcare system
Is research ethically and technically sound?	Who should target the population?	How to obtain informed consent	The burden to the patient and the family
Research methodology	Qualitative versus quantitative approach		
Subjective outcomes—quality of life (QOL)	Definition of the concept—global or health-related (HR)	Methodology of data collection—questionnaires or—interviews	
How to select and interpret HRQOL measures	Content validity	• clinical significance • data presentation • common metric	Outcomes during end-of-life care
Research funding	Need for specific programmes in clinical palliative care research		

boratively in order to improve the regulations to benefit this growing patient population. Palliative medicine should be taught in medical schools as a mandatory subject since all clinicians will be regularly confronted with the challenges of palliative care. By having the subject on the medical curricula, a necessary academic standard should be reached in the future.

2. Challenges

Most research in palliative medicine is descriptive in nature. Clinical practice is often based upon clinical experience, with little or no evidence from proper clinical research. Small descriptive non-comparative studies may be available; however, longitudinal studies with an optimal study design are rarely found in palliative care. Often evidence in palliative care is extrapolated from clinical research in the earlier phases of a disease. The limited amount of appropriate research probably reduces the chances for improvement of palliative care.

In most oncology trials, the primary aim of the treatment in a palliative stage of disease is prolongation of life, or prolongation of life combined with symptom control. For a new drug, or combination of drugs to have a realistic probability of effect, clinical trial inclusion criteria are often narrow, including patients with a good prognosis. Patients will often have few symptoms, an expected survival of more than 6 months, a WHO performance status better than two, age less than 70 years and a weight loss of less than 10% [2]. Clinicians have to be aware of the limited generalisablity of data from these studies for the palliative care population. Therefore, more research is needed to assess the effect of all types of treatment, including chemotherapy. Another example of the limited research performed in palliative care is the gap of knowledge about the most frequently-used drug in palliative care—morphine. More research is needed on the effects of the drug, its side-effects, and pharmacology in end-stage disease.

In palliative medicine, one of the primary aims is to relieve or prevent symptoms. Therefore, it is necessary to use valid and reliable outcome measures for these domains. In measuring subjective symptoms, there are many challenges related both to research and clinical practice. However, one should probably not restrict the outcomes to subjective indicators. Biological outcomes including changes in tumour burden, biochemical markers and other pathophysiological outcomes should also be used in palliative research, as they are in curative research. A better understanding of how treatment affects tumours, biological systems and improves symptom control, is needed. For example, it has been hypothesised that chemotherapy might results in symptom control without tumour shrinkage, theoretically by having effect on cytokines or other signal molecules [3]. In prospective palliative studies assessing the effects of chemotherapy in colorectal cancer, marginally improved survival and a major effect on quality of life have been found [4]. Furthermore, single fractions of radiotherapy are shown to have a similar effect on patients with bone pain, compared with traditional multiple fraction regimes [5,6]. The biological meaning of these empirical findings is not completely understood.

In addition to choosing the right outcomes, there are also challenges related to data collection, data analysis, research design, handling of missing data and general statistical considerations in clinical trials.

3. Patient population

There is an ongoing debate on how to define the target population in palliative medicine. Several variables are probably needed to target the population reliably (Table 1). In prospective studies assessing the effects of palliative care programmes, inclusion criteria have varied according to the institution, i.e. treated in hospice, home care, or oncology departments and also for individual patient characteristics, such as expected survival, tumour burden, symptoms, etc.

Treatment intention might be used as an indicator, meaning that the curative and life-prolonging treatment belongs to oncology, while palliation belongs to palliative medicine. Such an approach might be useful at an organisational level. However, it has several limitations on the patient level. In one study, it was found that approximately one-third of the patients in a representative sample in oncology departments received curative treatment, one-third received palliative symptom preventive treatment, and one-third received palliative symptomatic treatment [7].

These data indicate that using treatment intention as a selection criteria at a broad level might not be fruitful. Another approach is to define the population from the expected survival rates. By using prognostic indicators such as diagnosis, stage of disease, performance status and the patient's self-report of health-related quality of life (HRQOL), one might be able to target the population [8]. A third approach is to incorporate patients' needs and symptoms into the definition of the target population. In an Italian study, all the indicators—such as the level of symptoms, nutritional state, and treatment with corticosteroids and hospitalisation—were found to have indicative power on the patient's survival [9].

Palliative medicine has developed as a separate medical discipline, and so has palliative care as an integrated part of the healthcare system, or as an addition, for example, as free-standing hospices (Fig. 1). There is a continuous debate over what the specific elements of palliative care are, and which patients constitute the relevant population, from an idealistic, economical and scientific point of view.

It will probably not be fruitful to clearly define one part of the healthcare system as curative, another as focusing on prolongation of life, and a third on palliation. Methodologies and skills need to be integrated; however, it must also be acknowledged that certain types of skills and knowledge apply more for patients with a very short life expectancy, and specifically for patients who are dying. An integrated approach for end-of-life care—including symptom control, psychosocial and spiritual care, institutional as well as home care—are key elements in palliative care. In order to use the resources optimally during end-of-life care, the patient population needs to be targeted through valid indicators. One set of indicators must be related to life expectancy, others to symptom control and the patient's psychosocial and spiritual needs. There is a need for more research in this area, both from a meta perspective (healthcare system), individual perspective (where do I as a patient get optimal care?), and from a resource perspective (what are the 'markers' of a palliative care population?). Furthermore, the needs of the dying patient and the family in a multicultural society need to be scientifically addressed.

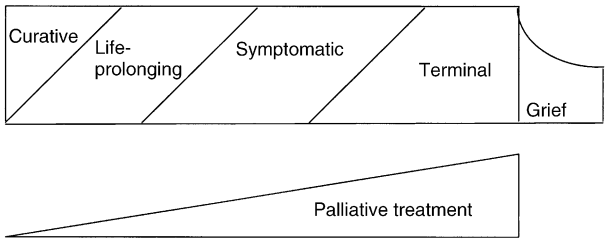

Fig. 1. Palliative care as an integrated approach in all stages of patient treatment.

4. General considerations on research in palliative care

Several arguments have been given to discourage clinical research in palliative care. It has been argued that the patient population is too ill and too vulnerable to allow meaningful scientific research. Secondly, it has been argued that there is not much more to learn, and that the accumulated wisdom is a good enough platform for clinical practice. Thirdly, the population is too heterogeneous for clinical research on a group level. A statement from Duncan Vere in the early 1980s might be used to shed light on the situation in palliative care: "Ignorance has risks, but they are largely unseen and unnoticed. Gaining knowledge has risks which are noticed, but largely unpredictable, and it is very costly (though less so than prolonged ignorance). It focuses blame, whereas ignorance dispels it. So maintaining ignorance often seems more attractive than gaining knowledge" [10].

Most doctors working in palliative care will agree on the need for research in this part of medicine. However, there are several problems related to performing research in palliative care in general, and specifically in a dying population. For example, who should target the patient population? How will you obtain informed consent? To what extent do you burden the patient and the family? Often in palliative care research (and in medicine in general) the healthcare staff, most often the doctor, is involved in targeting the population. Such a strategy leaves such people open to attack, and probably more so in palliative care because the doctor can easily be accused of either being too overly protective (paternalistic), thereby not asking patients to participate

in research; or too demanding towards the patients, thereby forcing them into research projects.

Our experience is that most patients are receptive to taking part in clinical research. The Declaration of Helsinki is generally accepted as an ethical code of practice for clinical research, and also applies to palliative medicine. Therefore, one might argue that not giving patients who are at the end-stage of life the opportunity to take part in clinical research is unethical. The palliative care team members might not be trained in research, and might even be sceptical of such an approach. Therefore, it is important to motivate and inform patients and caregivers. Discussion among the entire staff on research-related issues—specifically focusing on ethical challenges—should be a continuous conversation at all institutions performing research in palliative care.

If a study is approved by an ethical committee, it is not up to the participating clinician to re-evaluate patient inclusion in the project. Withdrawing patients who are eligible to participate in research might even be considered to be unethical.

A request for informed consent is mandatory. However, *how* to present the request to an imminently dying patient is not straightforward. Burdens to the patients and the families by asking them to participate in research should be considered; however, by being too restrictive, the doctor may be acting too paternalistic. More research is needed to understand the patient's wishes concerning participation in research, the attitudes of the staff, and how to properly obtain informed consent.

5. Methodology

Apart from the ethical challenges in palliative care research, there are several difficulties of a methodological nature. The patient population has multisystem affection with many simultaneous symptoms; limited survival and polypharmacy is also common. This pattern leads to difficulties related to trial design, outcome measures and compliance.

It has been argued that it is difficult to perform randomised, controlled trials in a palliative setting. However, some centres have shown that even in severely ill patients, such a study design is possible to perform, both in symptom control [11] and in the assessment of palliative care programmes [12,13].

The recruitment of patients into clinical trials is a challenge. Success is influenced by many factors, such as motivation and attitude of both the physicians and patients. In a palliative setting, terminal illness, complex symptomology and the patient's mental and physical exhaustion are likely to hinder trial entry. Another major obstacle in palliative care research is patient attrition or, in other words, decreasing sample size at subsequent assessments due to patients dropping out of the study. Reasons are varied, but the most important are patients' deaths or impairment due to progressive disease.

6. Health-related quality of life (HRQOL)

As stated in the WHO definition of palliative care, its goal is the achievement of the best possible QOL for the patients and their families. The use of QOL as an outcome is therefore self-explanatory. Most people have an intuitive understanding of this concept. It may be regarded as a positive term, conveying a person's subjective impression of his life and living situation. It often includes assessment of general satisfaction, fulfilment and happiness, as well as being in control and having a degree of independence [14,15]. Health is defined by the WHO as a "state of complete physical, mental and social well-being and not merely the absence of disease and infirmity". By combining these two definitions, the so-called concept of HRQOL has been developed, composed of scales and single items, measuring physical, mental and social components of health [16–18]. In palliative care, existential, spiritual, and family domains should be included as well [19, 20].

During the last decade, several HRQOL instruments have been tested in cancer clinical trials. Some instruments—such as the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [16,18], and the Function Assessment Cancer Treatment General Instrument (FACT G) [17]—are recommended by collaborative research groups. There appears to be a clear trend in improved research methodology, including elements such as analysis and interpretation of the data, presentation and discussion of the findings. However, there are still several problems related to these types of outcomes, such as content validity of the measures, clinical significance of the estimates, use of outcomes during end-of-life care, data presentation and a common metric (Table 1). Validated HRQOL measures are most often used in palliative chemotherapy and in palliative care—one of the most frequently used is the EORTC QLQ-C30. It is often supplemented by a disease- or domain-specific instrument. A variety of HRQOL instruments, such as the McGill Quality of Life Questionnaire, the Schedule of Evaluation of Individual Quality of Life (SEIQOL) [21], and checklist for clinical use Edmonton Symptom Assessment Schedule (ESAS) [22], have been developed specifically for palliative care. Important points of discussion are: What are the most relevant domains to be included in the instruments, the need for proxy ratings during end-of-life care, the variations of weighting of domains in the course of the disease, and how to select the appropriate instruments in different settings [23,24].

In a recent published study in patients with advanced cancer and a median life expectancy of 2 months, it was shown that patients completed HRQOL measures such as the EORTC QLQ-C30 until the last 1–2 weeks of life. There seems to be an urgent need for development of other types of methodology for imminently dying patients, probably using a more qualitative approach.

Studies assessing the impact of various models of specialised palliative care on quality of life exemplify the need for a critical evaluation of outcomes in palliative care research. In these studies, optimal palliative care was shown to have a limited or no positive effect compared with controlled interventions on HRQOL [25,26]. There might be several explanations for these findings. First, changes in palliative care organisations may not have an impact on patients' HRQOL, such as pain and fatigue. Outcome measures might not be sensitive enough to detect changes over time or between groups. Factors such as floor effects of the measures might explain this phenomenon.

HRQOL is, by definition, a multidimensional concept, and this multidimensionality of the outcomes might be a problem. Lack of well-defined endpoints among a wide range of outcomes may make it difficult to interpret trial results. There is a need to critically evaluate the primary and secondary endpoints in palliative care research.

It has been recognised that even in the area of pain research, there is a lack of uniformity in assessing pain. The EAPC Research Steering Committee acknowledges this, and has established an expert group to review the literature on pain assessment. Based upon their review, a set of guidelines has been published in order to establish a common approach to outcomes in pain research [27].

7. Research provides new important information

Evidence-based medicine needs to integrate the best individual's experience with available clinical evidence from research. Resource allocation in the healthcare system will probably rely on the evidence of effect even more so in the future. In order to receive proper resources in palliative care, interventions need to be proven to be effective. Such evidence is sparse in palliative medicine; therefore, research organisations on local, national and international levels need to be established.

Without proper financing for this type of research, further development in palliative care will not evolve. In competing with well-established applied clinical trial programs in Oncology, palliative care will lose the competition for research grants. Therefore, specific programmes supporting research on a European level in palliative care is needed.

8. European Association of Palliative Care—Research Network

The EAPC was established in 1988 as a multidisciplinary organisation and encompasses the patient, the family, the health care providers and the community. It is now a federation of 23 National Associations, and consists of approximately 23 000 members [28]. Within the EAPC, a Research Network is established.

The Research Network is working to improve palliative treatment through expert group recommendations based upon the existing literature and to perform multinational research. The first recommendations were published some years ago [29–31] and updated recommendations will be published soon. In addition, seven expert working groups are engaged in a variety of topics for which common European recommendations will be given [28]. The results of the work of these groups will be published in the near future.

Knowledge about the various palliative care programmes in Europe is lacking. In order to obtain valid descriptive data of the practice of palliative care across Europe and to introduce a broad spectrum of palliative care centres to collaborative research, the Research Network is now undertaking a descriptive study on palliative care programmes in European countries [28], aiming at:

- Identifying patient populations using specialised palliative care services in terms of demographic data, diagnostic groups, social circumstances and performance status in different European countries.
- Providing detailed information on the use of strong opioid analgesics and some other key drugs by specialised palliative care services.
- Identifying a network of palliative care services across Europe able to participate in collaborative research.

The next step will be to establish an infrastructure to perform collaborative prospective research and basic biological research within Europe.

One more important initiative to enhance research in palliative care is the organisation of a conference specially focused on providing and distributing information about research activities, and to invite health care professionals to participate in research. The 1st Congress of the Research Network of the EAPC was held in Berlin in December 2000.

9. Concluding remarks

It is our belief that patients in a palliative stage of disease, including dying patients, should receive treatment based upon an optimal diagnostic work-up, com-

bined with skilled nursing and the contribution of the multiprofessional staff, including specialists such as clergy, psychologists, social workers and physiotherapists, often in close collaboration with various medical specialities.

More research is needed to better understand the pathophysiology of the dying patients. Combined efforts between specialists in palliative medicine and researchers in the basic sciences are needed.

Clinical trials have a long history, and clinical trial methodology is well understood. It might be recommended that those designing studies in comprehensive palliative care, might pursue some of the following recommendations:

- Use highly trained data managers or research assistants for trial recruitment
- Use several recruitment techniques
- Monitor the recruitment rate
- Use simple referral routines that impose minimal workload on physicians
- Allow for substantial attrition when calculating the sample size
- Define inclusion criteria that allow a reasonable length of follow-up
- If defining HRQOL as an endpoint, consider using multi-item questionnaires for self reporting.

EAPC is an organisation capable of taking on collaborative clinical research in all areas of palliative care within the next few decades. This research needs proper economical funding in order to reach an acceptable quality and quantity.

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