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What influences participation in clinical trials in palliative care in a cancer centre?

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Abstract

Like any other speciality, palliative care needs a scientific foundation on which to base its practice. Research in palliative care is particularly difficult because of the characteristics of the patient population under study (e.g. advanced disease, poor performance status and limited prognosis). The aim of this paper was to highlight the challenges of recruitment into clinical trials in palliative care. Information on all patients treated at a specialist cancer centre who were referred for consideration of entry into any one of 23 clinical trials in palliative care was collected prospectively over 4 years to determine factors that influence patients to accept or reject entry into a study. Of the 1206 patients referred, 558 (46%) met the entry criteria. Of these, 362 (30%) agreed to enter and 248 (21% of all those referred) completed the study. Thus, 65% of all eligible patients were entered into trials but only 44% of these completed the study. The relatively high percentage of patients entered probably reflects the site (a cancer centre with a high research profile) and is not typical of other palliative care centres or hospices. The most common reasons given for unwillingness to participate were a wish to defer to a later date, a deterioration in condition, distance from home to hospital, a lack of interest, transfer to another unit, inability to give consent and family objection. In order to maximise patient accrual into trials in palliative care, studies should be designed to suit the patient population under study (e.g. be of short duration with realistic entry criteria) and not necessarily mirror the trial methodology of therapeutic trials in oncology.

Keywords: Research; Palliative care; Recruitment; Clinical trials; Consent; Cancer patients

1. Introduction

The need for research in palliative care has been well documented [1–3], but most practitioners within the speciality would acknowledge that research in this field is particularly difficult [4–6]. Recruitment to trials and research projects is often slow and further complicated by high attrition rates. The patient population is very unwell and nearing the end of life. Consequently, the problems experienced are complex physical, emotional and ethical ones. In an attempt to overcome some of the difficult recruitment problems, various research methodologies have been utilised with qualitative research becoming a popular option [7]. The pharmacological treatment of symptoms, however, still requires the use of quantitative research methodology often in the context of randomised controlled clinical trials (RCTs) [8].

Poor recruitment to clinical trials is not a problem that is exclusive to palliative care. Similar problems in recruitment to clinical trials in oncology have been reported [9]. Recognition of the difficulties in undertaking research in palliative care does not exclude the speciality from the 'rigours of scientific research'. On the contrary, palliative care needs a more scientific foundation upon which to base its practice [6]. Many of the 'treatments' which are widely used in this area are of unproven benefit [10]. Changes in healthcare funding have lead to a greater need to prove that the interventions employed in everyday practice, are not only efficacious and cost effective, but are based on scientific evidence [11]. Palliative care is not exempt from these conditions. Research has an important role in forming the foundations of what is a relatively new speciality.

In order to look for ways to improve recruitment of patients to palliative care clinical trials, it is just as

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important to understand why patients choose not to enter trials, as it is to understand why they do participate. This paper describes the experience encountered in recruiting patients to clinical trials within the Department of Palliative Medicine at the Royal Marsden NHS Trust, London and Surrey.

2. Patients and methods

The Royal Marsden NHS Trust is a specialist cancer centre situated on two sites. Each site has its own palliative care ward plus a hospital-wide support team. The Department of Palliative Medicine has an active interest in research. Regular research meetings are held to discuss proposed projects and to update current studies. Research projects undertaken include both pharmaceutical sponsored studies, and 'in-house' projects conceived and developed by both nursing and medical staff on the unit. There is a full-time palliative care research nurse on each site. Details of current research projects from the Department of Palliative Medicine are regularly circulated to consultants and senior registrars throughout the hospital. Similarly, the palliative care research nurses hold regular trial update teaching sessions and regularly visit other wards actively seeking out suitable patients to participate in studies. In this way, medical and nursing staff throughout the Trust are encouraged to refer both inpatients and outpatients for consideration of entry into palliative care studies.

For this survey, information on all patients referred to either research nurses for consideration of entry into palliative care clinical trials was collected prospectively over a 4 year period. All trials were of specific palliative therapeutic interventions rather than of the effectiveness of the palliative care service (Table 1). Data was collected using trial referral forms specifying patient name, age, hospital number, sex, diagnosis and the trial for which they were being considered. If in declining to participate, patients stated a reason, this was also recorded. However, patients were not required to give a specific reason for refusal.

The ultimate decision regarding whether an eligible patient was appropriate or well enough to enter a trial, was made by the research nurses after discussion with consultant staff in the Department of Palliative Medicine. This decision was based on factors such as the patient's general performance status, their comprehension of what the study entailed, their likely prognosis and their ability to complete all study procedures.

All patients referred for consideration of entry into any of the palliative care studies were included. All referrals were directed to the research nurses, thus preventing selection bias. In practice, the majority of patients participating in trials were in-patients on the palliative care wards or patients on other wards referred to the service for palliative care and/or symptom control.

The number of patients within each category, their median age, etc. was calculated from the trial referral

Table 1
Trials in progress in the study period

1	A pilot study to investigate the effect of 5HT3 antagonists on appetite and weight in advanced cancer patients with anorexia.[a,b]
2	The effect of oral bisphosphonates in prolonging time to recurrence of hypercalcaemia.[a,b]
3	The effect of 5HT3 antagonists on morphine-induced nausea and vomiting.[a,b]
4	A pharmacokinetic study of hydromorphone controlled release capsules.[a,b]
5	The use of corticosteroids to relieve bowel obstruction in patients with advanced cancer.
6	A survey of the benefit of blood transfusions in palliative care.[a]
7	A placebo controlled study of nebulised morphine in patients with breathlessness.
8	A placebo controlled trial of bisphosphonates for palliation of painful bone metastases.
9	A study of acupuncture in dyspnoea.
10	A comparison of transdermal fentanyl with sustained release morphine.[a,b]
11	The effects of high-dose morphine on glucocorticoid activity.[c]
12	A randomised dose finding study of bisphosphonates in hypercalcaemia.[c]
13	A comparison of oral phenazocine and oral morphine in the treatment of pain.[a,b]
14	A dose finding study of progestogens in cachectic cancer patients.[a,b]
15	A pilot study of inhaled steroids in cancer related lymphangitis.[c]
16	A comparison of once daily and normal release morphine in severe cancer pain.[a,b]
17	Theophylline in the management of cancer related breathlessness.
18	A comparative study of controlled release hydromorphone and morphine.[a,b]
19	A randomised controlled study of two co-analgesics in the treatment of neuropathic pain.
20	A dose finding study of bisphosphonates in the management of painful bone metastases.[c]
21	A survey of the use of alternative opioids in the palliative care setting.[c]
22	A long-term tolerability and efficacy study of long acting morphine in patients with pain.[a,b,c]
23	A phase II study of an anticonvulsant for the management of neuropathic pain.[a,c]

[a] Multicentre.
[b] Drug company sponsored.
[c] Trial ongoing.

forms. Further information (e.g. date of death) was obtained from the computerised hospital information system.

3. Results

In the period January 1993 to December 1996, 1206 patients were referred as 'suitable' for entry into one of the palliative care unit clinical trials. A total of 23 trials were in progress during the study period. The patients referred, 778 (65%) female and 428 (35%) male, represented a wide range of malignancies (Table 2) and were aged between 18 and 95 years with a median age of 60 years (Table 2). The median survival from time of referral to death in the 1111 patients in whom survival data could be obtained was 67 days (range: 0–1012+ days).

Of the 1206 patients referred, 648 (54%) patients were not approached as they did not fulfil the specified entry criteria (Fig. 1). 558 (46%) fulfilled the specified entry criteria, and after full discussion of the implications were asked to participate. 362 patients (30% of those originally referred) agreed, and gave informed consent. 248 patients (21%) completed the study period (Table 3). Thus, 65% of eligible patients were entered into clinical trials and of these, 44% completed all study procedures. 196 eligible patients (35%) did not participate. Reasons for declining participation were given in 163 cases (Table 4). In reality, if all such cases were recorded, this figure would be much higher.

Table 2
Patient characteristics

	n patients *n* (%)
Sex	
Male	428 (35)
Female	778 (65)
Age (years)	
18–39	88 (7)
40–59	491 (41)
60–79	551 (46)
⩾80	59 (5)
Unknown	17 (1)
Median (range)	60 (18–95) years
Diagnosis	
Breast	400 (33)
Lung	199 (17)
Gynaecological	137 (11)
Gastrointestinal	84 (7)
Genitourinary	75 (6)
Prostate	70 (6)
Haematological	70 (6)
Unknown primary	43 (4)
Head and neck	43 (4)
Sarcoma	27 (2)
Other	40 (3)
Unknown	18 (1)
Total	1206 (100)

4. Discussion

The problems and pitfalls of undertaking research in palliative care effectiveness have been illustrated in a paper by McWhinney and colleagues [12]. This led to a call for papers highlighting methodological difficulties in palliative care research [13]. It is hoped that this paper might aid further research in the area by documenting the issues encountered in attempting to undertake research in palliative care within a large cancer centre.

These recruitment figures, although taken from patients requiring palliative care, are unlikely to be truly representative of the palliative care population as a whole, as they are taken from a specialist cancer centre where there is a high research profile. All the 'mechanics' for conducting clinical trials are in place (for example, ready access to diagnostic facilities, in-house statisticians, software for data collection and regular scientific and ethics committee meetings). Research is actively encouraged and positively supported. Patients referred for palliative care are often seen at an earlier stage in their disease than those in other palliative care settings (for example, the community or local hospice), and consequently will often have relatively stable disease, better general health and performance status. They are, therefore, more able to comply with and complete the various study procedures. Moreover, the presence of two full-time research nurses, dedicated to palliative care research, and available to review patients and collect data will have facilitated recruitment considerably.

Why do patients agree to enter? 362 (65%) of the patients meeting the eligibility criteria agreed to entry. This figure is considerably higher than that in oncology trials where less than 5% would be expected to enter [9]. This high acceptance rate may well reflect the specialist

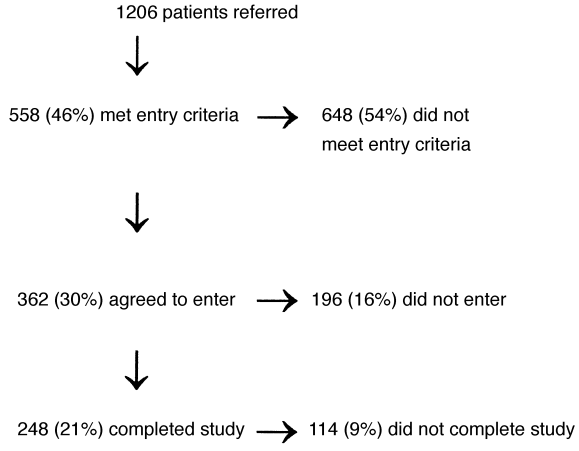

Fig. 1. Outcome of patients referred.

Table 3
Number of patients referred for each trial and outcome

n patients Trial	Trial title	Referred *n* (%)	Eligible *n* (%)	Entered *n* (%)	Completed *n* (%)
1	Anorexia and appetite	18 (1)	5 (1)	4 (1)	0
2	Oral bisphosphonates and hypercalcaemia	15 (1)	11 (2)	7 (2)	0
3	5HT3 antagonists and opioid-induced nausea	30 (2)	13 (2)	12 (3)	4 (2)
4	Pharmacokinetics of hydromorphone	31 (3)	13 (2)	8 (2)	8 (3)
5	Steroids in bowel obstruction	33 (3)	17 (3)	14 (4)	12 (5)
6	Blood transfusions	20 (2)	19 (3)	19 (5)	17 (7)
7	Nebulised morphine for dyspnoea	97 (8)	70 (13)	56 (15)	53 (21)
8	Bisphosphonates for bone pain (1)	40 (3)	17 (3)	12 (3)	6 (2)
9	Acupuncture for breathlessness	27 (2)	24 (4)	24 (7)	20 (8)
10	Fentanyl compared with MST	100 (8)	65 (12)	38 (10)	24 (10)
11	Glucocorticoids and morphine	17 (1)	4 (1)	3 (1)	0
12	Hypercalcaemia dose finding study	228 (19)	101 (18)	67 (19)	57 (23)
13	Phenazocine compared to morphine	4 (0.3)	3 (0.5)	2 (1)	2 (1)
14	Cachexia study	111 (9)	36 (6)	11 (3)	1 (0.4)
15	Inhaled steroids for lymphangitis	38 (3)	17 (3)	13 (4)	6 (2)
16	Once daily compared with twice daily morphine	62 (5)	20 (4)	6 (2)	3 (1)
17	Theophylline for dyspnoea	46 (4)	7 (1)	3 (1)	0
18	Hydromorphone compared with morphine	102 (8)	29 (5)	10 (3)	4 (2)
19	Neuropathic pain	37 (3)	10 (2)	5 (1)	2 (1)
20	Bisphosphonates for bone pain (2)	65 (5)	26 (5)	22 (6)	16 (6)
21	Alternative opioids	21 (2)	18 (3)	16 (0.3)	6 (2)
22	Once daily morphine	45 (4)	23 (4)	4 (1)	3 (1)
23	Anticonvulsants for neuropathic pain	13 (1)	7 (1)	3 (1)	1 (0.4)
	Not stated/miscellaneous	6 (0.5)	3 (0.5)	3 (1)	3 (1)
Total		1206 (100)	558 (100)	362 (100)	248 (100)

cancer centre as discussed above. Many of the patients would have already participated in clinical trials at some stage during their treatment course and the Royal Marsden is well known as a research centre. Patients often feel they are 'giving something back' or helping others in agreeing to participate. They will often have seen other patients participating in trials with the perception that they received more individual attention because of it. Participation in a study may also be a way of holding on to medical attention and avoiding discharge. Agreeing to enter a study may help patients feel justified in their wish to remain in hospital. Slevin and colleagues [9] found that 42% of oncology patients were enthusiastic about entering clinical trials, wanting to be treated by a doctor with a specialist interest in their condition and encouraged by the fact that their disease was likely to be closely monitored.

Table 4
Reason stated for eligible patients declining participation in trials

Reason	*n* (%)
Patient prefers to wait before entry	34 (17)
Too unwell/deterioration in condition	32 (16)
Lives too far away	21 (11)
Patient 'didn't want to'/'not interested'	15 (8)
Transfer to hospice/hospital/discharge	11 (6)
Unable to give informed consent	11 (6)
Family objection	10 (5)
Objection to medication	7 (4)
Patient not willing/unable to complete forms	6 (3)
Doctor error/objection	5 (3)
Too many pills	4 (2)
Too anxious	3 (2)
Weekend/evening admission (research nurse unavailable)	2 (1)
Placebo fear	1 (1)
Previous participation in trials	1 (1)
Declined consent reason unknown	33 (17)
Total	196 (100)

It has been suggested that the poor accrual rates of oncology patients to clinical studies does not occur because patients refuse but because of a failure of both physicians to seek recruitment and of the health-care system to make it easy for them to do so [14]. The figures presented here suggest that if asked, a high proportion of patients will agree to participate in research. It is the eligibility criteria that seem to be the main 'stumbling block'. Of the 1206 patients referred only about half (46%) actually fulfilled the entry criteria, or were considered well enough to enter.

It may be that palliative care as a speciality has relied too much on oncology as a role model for the basis of its clinical trials. Patients receiving specific anticancer therapies are generally of reasonable performance status whereas palliative care patients are often in poor health and limited in their activities. For example, it is often meaningless to make a specific life expectancy an inclusion criteria. The prognosis of this group of patients will

always be limited (as illustrated by the median survival of only 67 days (0–1012+) from time of referral in this study). Moreover, estimates of life expectancy in this group are notoriously poor [15] and may wrongly exclude some patients. Similarly, trials of malignant disease usually have 'hard' end-points such as objective response in the form of a measurable tumour mass, whereas palliative care trials generally consider more 'nebulous', difficult to measure end-points, for example, control of pain or nausea. It should be noted, however, that considerable progress has been made in recent years to reduce the subjectivity of these measures by the development of robust and well validated tools to measure symptoms such as pain [16].

Consideration should be given to the well-documented high attrition rates [4]; a study duration of more than 1 month is generally not feasible as many patients will have died or become too unwell to participate or die within 2 months. It is noteworthy that 31% (114/362) of the patients who were accrued did not complete the study, usually because of a deterioration in health or performance status. Only 44% of patients entered completed all study procedures.

The emphasis in palliative care research should be on the development of more realistic studies which are both practical and achievable in this poor performance status population, rather than aiming for the few patients who have stable disease, controlled symptoms and who are likely to survive for the required trial period. It has been suggested that patients should be involved in the development of protocols and the setting up of research agenda [17]. This is an obvious way of ensuring that trials in palliative care remain 'patient friendly'. Thirteen of the studies originated from the particular research interests of the various consultants and senior registrars. Recently we have undertaken studies developed by members of the nursing staff. To date, no trial has been undertaken in direct response to a particular patient need.

Ten of the 23 trials (43%) presented here originated from pharmaceutical companies wishing to trial new products or new indications for established drugs. Clinical trials are expensive to run, especially when research personnel are employed. This can result in a dependence on external funding from pharmaceutical companies, especially when many palliative care patients are cared for by hospices and community teams funded primarily from charitable sources. Palliative care research programmes can thus, to a certain extent, be agenda driven with the questions asked and methodology used influenced by the requirements of the pharmaceutical industry.

The ideal trial design in palliative care needs to reflect clinical practice, have wide inclusion and exclusion criteria, few extra hospital visits, be of short duration, of multicentre design and use simple brief assessments. Tannock [14] suggests that some flexibility in evaluating strategies might also encourage recruitment. Over the 4 year period under study, the design of trials in this unit have evolved to become more realistically suited to the population under study.

The short overall median survival time from referral to death (67 days) indicates that many patients were asked to participate in research in the latter stages of their illness. To some extent, this is inevitable when studying symptoms frequently seen in the terminal phase of disease, such as dyspnoea, pain control and hypercalcaemia. Attempts are usually made to ensure that palliative care patients with a limited prognosis have to spend as little time as possible in hospital. A consideration for any researcher in palliative care should be whether participation in research leads to extended or extra hospital admissions.

Why do patients refuse to participate? In general, patients did not seem to be afraid to decline participation. In this survey, only 15 patients refused outright, although 34 patients declined participation at the time preferring to enter later. This may be a way of 'keeping the doctors happy', ensuring continuing care and declining without actually having to say no.

Family objection to clinical trials was not a common factor (10 cases) as the reason for not participating, but may have been a reason for non-referral in the first place. It is important that families and carers do not feel that their relation is being used as a 'guinea pig' or being included in an unnecessary experiment. Palliative care claims to encompass the care of both the patient and their family; this approach is equally important when recruiting patients to clinical trials. Ongoing communication with relatives during the explanation and informed consent procedure and the provision of written information may help to alleviate this problem [19,20].

It has been suggested that staff employed in palliative care often enter the speciality for humanitarian reasons, which can lead to resistance when research issues are raised [18]. This 'gate-keeping' patient protection phenomena is not reflected in the figures shown in this study as only patients who were actually referred are included. It is likely, that some eligible patients were not referred because members of staff felt that they should not be subjected to the procedures involved in the various studies. Similarly, the method of referral for entry into studies was not robust, and often dependent on the actual searching out of suitable patients by the research nurse. Outside the palliative care wards, referral will often depend on the particular interests and experience of individual doctors. It is likely that only a very small proportion of eligible patients throughout the hospital are referred. Ongoing education is an integral part of the palliative care team approach and it may be that more teaching about the benefits of research in the field is necessary to help rectify these problems.

As a major cancer centre, the Royal Marsden NHS Trust is referred a large number of patients who do not live in the local area. This precluded a number of patients from entry (11% of those eligible) and is particularly relevant if follow-up visits are required. The problem could potentially be addressed by closer liaison with community services, or through a wider network of multicentre studies. One of the ways of overcoming poor patient accrual into trials in palliative care is to consider multicentre participation [5]. This is not without problems however and is dependent on the 'equal enthusiasm' of all centres and as mentioned above, on funding issues. Twelve studies (52%) in this review were multicentre and of these, 10 were pharmaceutical company sponsored trials. This may reflect the high cost of running a multicentre study successfully or the practical difficulties in co-ordinating research at several different sites.

5. Conclusions

Whilst fully supporting the multidisciplinary nature of palliative care, it remains true that for many patients, drug therapy remains of fundamental importance in maintaining symptom control and quality of life. Many new drugs and drug formulations are becoming available and many of the older established drugs are used on the basis of anecdote or physician preference without a strong evidence base. The optimal use of these medications will often warrant a clinical trial.

The results of this paper suggest that on the whole palliative care patients do not object to research nor do they refuse to participate in clinical trials if asked. Inappropriate eligibility criteria in many studies seems to present the major problem for patient accrual. Good quality quantitative research in palliative care is difficult, but not impossible. To be successful, it is essential that studies are designed to suit the particular characteristics of the patient population under study and need not necessarily mirror studies in oncology.

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