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Clinical trials to study pain in patients with advanced cancer: practical difficulties

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Cancer is a common cause of death in our society and associated pain is prevalent in cancer patients. Despite this, pain is often not treated optimally. Although education (patient and caregiver) might improve the situation, many difficulties remain in carrying out clinical trials of new drugs or therapies in this particular group of patients. Appropriate controlled clinical trials need to be designed to maximise validity (randomised, blinding, quality of collected data, enough evaluable patients, statistical analyses) and effectiveness. Patient numbers are often small, the diseases and mechanisms of pain non-homogenous, and assessment techniques and analgesic requirements (and tolerance) may be variable. Furthermore, pain may be unstable, polypharmacy is often involved, behavioural and other cognitive factors may change, patient compliance may be suspect, and side effect profiles may be difficult to interpret (disease, patient status, polypharmacy). Strategies that may increase validity constrain the feasibility of the study and the generalisability of the study results obtained.

Introduction

Cancer is a common cause of death in our society. In Canada, cancer accounts for just over one in four deaths;[1] of every five deaths from all causes in the United States, one is from cancer.[2] In spite of much progress in cancer treatment research, fewer than 50% of all cancer patients in North America (excluding non-melanoma skin cancer) can expect to be alive and free of disease 5 years after diagnosis.[3]

Patients with advanced cancer may present with a complex array of symptoms, of which pain is the most prevalent.[4] There have been no large-scale national epidemiological studies of the incidence and severity of pain in cancer patients, but small-scale studies suggest that moderate or severe pain is experienced by one-third of cancer patients receiving active therapy and by 60%–90% of patients with advanced cancer.[5] In Canada, approximately 80,000 patients suffer pain due to cancer every year;[6] in the United States, using data from 1983, it has been calculated that 297,000 patients dying with cancer and 1,027,000 cancer patients who survived that year had pain.[7]

In the past 20 years, palliative care services, mostly for advanced cancer patients, have expanded rapidly, but the study of pain control in this population has until recently been a neglected issue. As a result, pain treatment has been largely empirical, inadequate, and resulted in unnecessary suffering for many patients.[8] While worldwide guidelines for pain treatment in cancer patients have now been issued by the World Health Organization (WHO),[9] more effective and flexible means of pain control are needed. This necessitates evaluations of the effectiveness and safety of old and new drugs, and of new routes of administration.[8] In spite of the urgent need for more knowledge in this area, pain research is carried out by relatively few isolated groups and, aside from psycho-oncology, large studies employing double-blind trials with good characterisation of subjects and symptoms are lacking.[3]

That this has been the case is not surprising, considering that research in cancer pain has been severely underfunded.[8] In addition, studies in terminal patients face obstacles not found in other medical conditions or other types of pain. These arise from the heterogeneity of cancer patients, the complex nature of the pain associated with their condition, and their relatively short life-span. Despite this, aside from the guidelines issued by the WHO, the Agency for Health Care Policy and Research (AHCPR) in the United States has recently issued a Clinical Practice Guideline on the 'Management of Cancer Pain' based on 'Type of Evidence'.[10] Although a significant educational resource for clinical practice, future improvements in care will also require further clinical research. This

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paper will review some of the constraints inherent in research of pain in cancer patients.

Requirements of appropriate clinical trials

Sound, scientific methodology in the evaluation of new therapies demands controlled clinical trials carefully designed to maximise validity (i.e. the results are true), generalisability (i.e. the results are widely applicable) and effectiveness (i.e. the trial is feasible and affordable).[11] Fulfilment of the first requirement requires the use of randomised, double-blind trials, a high quality of collected data, appropriate statistical analyses, and enough evaluable patients to identify true differences between treatments. These requirements are difficult to meet when investigating pain therapies in terminally ill cancer patients.

A basic need of controlled clinical trials is that the baseline characteristics of patients assigned to different treatments are similar.[12] Theoretically, randomisation ensures that there is an unbiased distribution of patients in each of the treatment groups. In practice, given the great biological variability in humans, it is difficult to have well balanced treatment groups unless the number of patients is large. This difficulty is compounded in terminal cancer patients with pain whereby large groups of patients with equivalent enrolment and treatment criteria are difficult to attain. Therefore, new approaches need to be considered to deal with this important but difficult problem.

Pain in cancer

Unlike other populations with well defined, homogene-ous disease, cancer patients suffering from pain present with a variety of tumours, unstable disease, and complex pain profiles. Although there is no information linking biological characteristics of tumours with their propensity to induce pain,[3] some data have identified that particular types of tumours are more likely to produce pain than others[13] and that the overall severity of pain is associated with tumour type.[14,15]

Pain associated with cancer may have three different aetiologies: the cancer itself (tumour infiltration of pain-sensitive structures; vascular occlusion by tumour); cancer therapy (injury to nerves, bone and soft tissue as a result of chemotherapy, radiation therapy, or surgery); or, less commonly, may be unrelated to cancer or its treatment (low back pain, osteoarthritis, headache, etc.).[5]

Most causes of pain are related to tumour growth.[16,17] Daut and Cleeland[13] reported that patients with metastatic cancer were more likely to report pain and higher pain intensity than those with non-metastatic cancers. In an investigation of the causes of pain in 200 patients referred to a cancer clinic, Banning *et al.*[18] found pain caused by tumour growth (i.e. 'the neoplastic lesion causes nociception directly') in 158 patients, pain secondary to cancer or its treatment (i.e. 'pain was a consequence of tumour growth or treatment, but neoplastic tissue was not directly involved in the nociceptive process') in 116 patients, and pain unrelated to cancer in 33 patients.

However, the pain experienced by cancer patients can have several sources. In the 200 patients surveyed by Banning *et al.*,[18] 37 patients presented with one pain cause, 57 patients with two, 44 patients with three, and 48 patients with four or more pain causes. Seventeen patients presented with pain from all three; only three patients had pain unrelated to cancer or treatment. Twycross and Fairfield[19] reported that 80% of 100 patients referred for hospice care experienced two or more anatomically distinct pains (range 1–8).

An alternative classification distinguishes among discrete pain syndromes. The most common, syndromes associated with infiltration of bone, include involvement of the base of the skull, the vertebral bodies and the sacrum. In each group, patients present with very typical symptomatology. There are also typical pain syndromes associated with direct infiltration of nerve tissue (e.g. pain in the retroperitoneal or intercostal areas followed by motor deficits, and brachial plexopathy). Other pain syndromes related to cancer therapy (surgery, radiotherapy and chemotherapy), which may occur in the absence of active tumour, also have specific characteristics.[20] Finally, there are pain syndromes unrelated to cancer. Accurate data regarding the prevalence of each syndrome in the pain population are not available, but this classification is useful clinically.[7]

Another classification of cancer-related pain, based on the pathophysiology of pain, subdivides pain as somatic, visceral and neuropathic in origin.[21] Somatic and visceral pain involve direct activation of nociceptors and are often a complication of tumour infiltration of tissues, or of tissue-damaging effects of cancer therapy. Constant and well localised, somatic pain results from activation of nociceptors in cutaneous and deep tissues (e.g. tumour metastasis in bone) and is the most common type of pain in cancer patients. Visceral pain results from stretching or distension of the viscera or the production of an inflammatory response with release of algesic chemicals in the vicinity of nociceptors. This type of pain is usually poorly localised and is often described as deep squeezing and pressure-like, and when acute is

associated with autonomic dysfunction (nausea, vomiting, diaphoresis). It may be referred to cutaneous sites, often remote from the site of the lesion.

Neuropathic pain is most often a complication of tumour infiltration of large peripheral nerve trunks, but may also be a complication of cancer therapy. This type of pain is mediated by non-nociceptive mechanisms and may or may not involve the sympathetic nervous system. Pain resulting from neural injury is often severe, typically described as a constant, dull squeezing and aching sensation, with superimposed paroxysms of burning and/or electrical shock-like sensations.[21]

Although this classification is useful, the clinical and pathogenetic characteristics of cancer pain and its response to analgesic treatment have not yet been firmly established.[22] According to some authors, neuropathic pain responds poorly to opioids, but this has been questioned by other authors.[23] Neuropathic pain may have some nociceptive components apart from deafferentation pain, which may be responsive to opioid treatment, but this is still controversial.[24]

It is important to keep in mind, however, that a single cancer patient may present with a mixture of pain categories and may need more than one type of treatment approach to attain adequate analgesia. In addition, some types of pain may not be amenable to classification.[24]

Analgesic requirements

Another factor complicating the study of pain in cancer patients is the marked variability in dose and response to analgesics. Individual requirements vary from patient to patient and also within patients. In a retrospective survey of a group of 90 cancer patients during the last 4 weeks of life, Coyle *et al.*[25] found that total opioid consumption ranged from 7 to 35,164 i.m. morphine equivalent milligrams. Thirty per cent of the patients exhibited stable opioid requirements, and 14% had a stepladder increase; three other patterns of opioid requirements were identified but the changing needs of an individual patient could not be predicted. Furthermore, some patients (17%) required more than one opioid medication and 53 patients (59%) needed more than one route of administration. Some exhibited a rapid escalation of narcotic use before death.

Kanner and Foley[16] also found that as illness progressed, cancer patients' opioid requirements increased. Morris *et al.*[15] reported more frequent continuous pain and severe pain with progressive illness. Increased requirements may therefore be due to increases in pain severity with progressive malignancy.[26] This would necessitate relatively short time limits when considering evaluation periods, particularly during crossover designs.

Part of the variability in the response of patients with cancer pain to opioid drugs relates to characteristics inherent in the pain.[27–29] As mentioned above, nerve damage pain, or deafferentation pain, has been singled out in this context; in addition, activity-related (incident) pain, muscle spasm pain, many forms of headache and tenesmoid pain are characteristically difficult to treat with opioids,[30] such that a completely pain-free state may not be possible in many patients with advanced cancer.[7,14,15]

Variability in response may also be associated with pharmacokinetic factors. Unfortunately, very little hard data exist in this area. Decreased clearance of morphine in patients over 50 years of age [31,32] may explain in part why older patients appear to be more sensitive to opioids. Renal impairment dramatically enhances opiate toxicity,[3] possibly because some of the opioids have active metabolites dependent upon renal excretion.[33] On the other hand, patients with severe hepatic damage may take opioids without difficulty (although opioids are primarily metabolised by the liver), possibly because of significant extrahepatic metabolism.[32]

The development of tolerance is another factor to consider regarding opioid responsiveness; this phenomenon develops at different rates for various narcotic effects. Tolerance to respiratory depression develops rapidly, unlike tolerance to the constipatory effects of narcotics, which may never develop. Cases of patients receiving very high doses of narcotics without respiratory compromise or sedation have been recorded.[26] Aside from tolerance *per se* which is not likely to be a major problem in patients with stable disease and pain, disease progression or complications of disease (e.g. pathologic fracture) are more likely to be causes of continued dose escalation. The use of the term 'tolerance' to describe this phenomenon has to be separated from the development of true tolerance *per se*.

Opioid tolerance may also be associated with previous opioid intake;[26,34] this may be critical in clinical research. Some people are more susceptible to developing tolerance than others. For example, in patients receiving subcutaneous narcotics, 15% required a daily increase $\geq 5\%$ of the initial dose compared with the mean daily increase of $2.4\% \pm 1.6\%$.[35] Genetic variability in opioid response, shown in animals, may also occur in humans.[23] Patient age may also be a factor. Kaiko *et al.*[36] showed that older patients were more sensitive to opioids. Morris *et al.*[15] reported a significantly lower proportion of terminal cancer

patients ≥ 75 years of age with persistent pain and a higher proportion of patients of this age free of pain compared to younger patients. It is not clear if differences in perception of these symptoms are physiological or culturally conditioned.

Although all patients with chronic pain may experience psychosocial distress, these effects are more pronounced in patients with cancer. Cancer patients with pain may develop greater emotional reactions of fear, anxiety, reactive depression, hypochondriasis and neuroticism to the pain than other chronic pain patients.[37,38] Many of these problems may be related to fears concerning the progression of their underlying cancer. Patients with severe emotional, spiritual and psychological problems exhibit opioid resistance which may only be overcome if the emotional aspects of pain are addressed.[23,30] Patients with a history of psychological dependence may also exhibit opioid resistance, but other factors, such as undermedication due to misconceptions from health workers, may be partly responsible.[17]

Pain instability

Pain in cancer patients is not stable throughout the day. Breakthrough pain (pain occurring intermittently and being more severe than baseline pain) is fairly common in cancer patients. As a result, common practice dictates that even patients receiving slow-release preparations (e.g. MS-Contin) require extra immediate-release morphine to deal with these episodes of breakthrough pain. Portenoy and Hagen[39] have analysed this phenomenon in patients with chronic pain managed with opioid drugs. The prevalence of transitory flares of pain (severe or excruciating) in patients who have achieved the criterion of stable opioid dosing for two or more days was 64% (41 out of 63 patients); 51 different pains were described (median of four pains per day). There was a large variability in terms of the number of breakthrough pain episodes, duration, quality, aetiology and pathophysiology. Most patients described from 1–10 breakthrough pain episodes per day, but five patients had more than 10 episodes. Median duration of pain was 30 min (1–240 min); breakthrough pain usually occurred in the same location as the continuous pain experienced by each patient. In 15 episodes of breakthrough pain (29%), onset occurred at the end of the dosing interval of the regularly scheduled analgesic (mostly opioids), in some cases in association with precipitating factors.

Factors precipitating breakthrough pain were identified in 28 (55%) of the 51 different pains. Most were volitional (incident pain) and included: movement in bed, walking, coughing, sitting, standing and touching. For 23 (45%) of pains, no precipitant could be identified.

Aside from breakthrough or incident pain, the background pain intensity (as measured by Visual Analogue Scale) may also vary during the day with specific individual patterns. This may necessitate the measurement of pain intensity at several specific periods of the day. However, although the background pain intensity may not change, there may be changes in analgesic consumption based on factors that may change the number of episodes of incident or breakthrough pain. The combination of pain intensity scale with analgesic consumption figures may have to be used with some caution.

Selection of stratification of patients with cancer pain

Given the excessive variability in cancer patients with pain, strategies must be used to reduce heterogeneity of treatment groups in clinical studies. One conceivable strategy would be to select patients with specific characteristics, such as type of tumour or pain syndrome. This would increase the validity of the study but at the extent of effectiveness, i.e. would enough patients meeting the narrow criteria be accrued in a reasonable time? Furthermore, the results would not be applicable to other cancer patients with pain.

Another strategy would be to stratify patients prior to randomisation (or to do co-variance analyses) according to factors such as tumour type or pain category, specific cancer pain stage, factors associated with analgesic requirements, or incidence of breakthrough pain. While stratification provides a better balance between treatment groups, it increases the complexity of the trial and the need for a larger sample size, and reduces the degrees of freedom.[12,40] Additionally, overdoing subset analyses increases the risk of spurious results produced by chance effects alone.[40,41]

An alternative approach to reduce stratification to a manageable size would be to categorise patients into a limited number of strata on the basis of a constellation of variables.[42] A standardised staging system of cancer pain that could be used for such purposes, analogous to the ones developed to classify various malignancies, is not as yet available.

A group in Edmonton, Canada, reported a preliminary study in which cancer patients with pain were classified into three prognostic categories according to mechanism of pain, pain characteristics, previous narcotic exposure, cognitive function and psycho-

logical distress.[24] With this staging system they were able to predict a patient's response to pain control according to pain stage. After refinement and validation, this system may be useful to attain baseline equivalency in cancer pain clinical trials and to enable valid comparisons of studies among different research groups. Such a system (analogous to treating patients with different stages of cancer with different treatments) would be an important advance, as at present it is difficult to compare treatment methods in pain studies because of inadequate pain characterisation. Likewise, analgesic doses used in different studies are difficult to compare, as dose equivalency tables used by different researchers vary. For example, compared to standard morphine 10 mg i.m., equivalent doses for oral morphine are given as 20–30 mg by Health and Welfare Canada [6] and as 60 mg in commonly used medical textbooks.[5,43] Likewise, equivalent doses for hydromorphine are given as 2 mg i.m. and 4 mg p.o. in the Canadian monograph and as 1.5 and 1.3 mg i.m. and 7.5 mg p.o. in the medical textbooks. Some consensus needs to be achieved regarding dose equivalency among various narcotics to allow more appropriate comparisons between published studies.

Study design

Researchers must carefully evaluate the advantages of using either crossover or parallel study designs to ensure validity without compromising effectiveness. Crossover designs are used to increase the sensitivity of a study by using each patient as his own control. This increases validity and reduces the sample size required compared with parallel group studies of the same statistical power.[44]

An important assumption in crossover studies is that the disease is stable over the time of the study. This approach would be clearly inappropriate in long-term studies of patients with advanced cancer, the majority of whom continue to have underlying disease progression. Therefore, if a crossover design is used, the study would have to be of relatively short duration. Other assumptions in crossover studies are that the therapeutic effects of the medication cease soon after it is discontinued during a washout period and that its effects would not differ whether it was given first or last. In cancer patients receiving narcotics, a washout period is not possible since it would be unethical to abruptly withdraw and withhold analgesic medication during the washout phase. Fortunately, opioid tolerance does not develop quickly over short time periods in patients who already have been chronically treated with narcotics.

Parallel designs are less dependent on assumptions about disease progression. They are appropriate for patients' whose conditions may change over the longer period needed by a crossover study, where there may be carryover effects, or where it is reasonable to assume baseline homogeneity between treatment groups (or when precautions such as stratification and blocking have been taken to attain it).[45] In cancer patients, this last condition may be extremely difficult to achieve as discussed earlier; additionally, a large number of patients may be needed to attain the desired statistical power. However, the duration of the study need not be as long as in a crossover study and the dropout rate may be smaller.

The use of placebo to demonstrate efficacy of a new drug or drug formulation would be unethical in trials with cancer patients and comparisons would have to be made with an analgesic standard. However, unless the drug tested represents a major breakthrough in the treatment of pain, a very large patient sample would be needed to demonstrate a clear-cut superiority over the standard. More likely, the differences between treatments would be relatively modest in comparison to the variability between patients and would therefore remain undetected.

Inclusion criteria and accrual of patients

Researchers planning a study to evaluate pain treatment in cancer patients face a dilemma when it comes to patient accrual: the sample population studied should resemble that population that will be benefiting clinically from the treatment tested. However, this is not easily accomplished with cancer patients. Investigations frequently study patients who are more stable than those who would ultimately benefit from new treatments. Most trials of long-acting morphine preparations used stable patients requiring an overall low dose of narcotics.[46–49] The results might not be applied to populations of patients with severe pain, who require much higher doses of narcotic and have significant impairment of gastrointestinal motility.[50] For example, patients with low narcotic needs may be treated satisfactorily with MS-Contin on a q 12 h schedule, while patients on a high-dose schedule frequently may require a q 8 h schedule. This is in contradistinction to the earlier published trials suggesting that a q 12 h schedule be recommended.

Patients participating in clinical trials must meet inclusion criteria that necessitate the exclusion of those with significant cardiac, hepatic, pulmonary or renal disease, or encephalopathy. This might limit the

relevance of the results obtained when applied to advanced cancer patients. To make the results of trials more generalisable, it may be necessary to extend the range of 'acceptable' values (e.g. bilirubin, creatinine) for patient inclusion into these trials. However, decisions regarding the level of clinical dysfunction at which patients are still eligible for participation in clinical trials rely on the clinical judgement of researchers and are a source of bias.[51]

Selection of participants on the basis of factors predicting compliance with record keeping may further restrict how representative the sample will be from the target population. Participants must demonstrate performance standards that may be too rigorous for many patients at this stage of their illness. McCusker[52] found that, at the onset of the terminal care period, 84 (69%) of 122 patients were either 100% bedridden or bedridden for more than 50% of the time. Patient selection would also rule out a large proportion of terminal cancer patients who may not be able to respond to the demands of a clinical trial because of impaired cognitive function or affective disorders. Impaired cognitive function may be present in cancer patients as a direct consequence of the cancer or as a result of its treatment. It is often found in subtle form and misdiagnosed as depression;[53,54] its prevalence is difficult to assess. Depression is also common in cancer patients and its severity may increase as the disease progresses. A study of 334 patients referred for psychiatric consultation for evaluation of depression or suicidal risk[55] found that of the 162 patients (48.5%) who were given a diagnosis of depression, 38 (24%) presented with severe and six (5%) with extreme depression. All patients with severe or extreme depression had advanced cancer, and many were in a pre-terminal state. In addition, 84 patients (24%) had cerebral dysfunction related to steroids or other drugs, or to metabolic derangement.

Derogatis *et al.*[56] assessed psychiatric disorders in 215 randomly accessed hospitalised and ambulatory adult patients with cancer and reported that of the 47% with clinically apparent psychiatric disorders, the majority (68%) had an adjustment disorder with depressed, anxious or mixed mood; 13% had major depression and 8% an organic brain syndrome. Personality and anxiety disorders accounted for the rest. In a study of 100 patients admitted to a tertiary care hospital, 10% had memory problems, 11% suffered from confusion and 31% from depression,[4] all conditions likely to interfere with accurate response to interviews and record keeping.

Metabolic abnormalities and losses of function occur progressively. Thus, many patients who initially may meet inclusion criteria but are at or near borderline may rapidly deteriorate during the study, especially towards the last 3 weeks of life[57] and have to be withdrawn from the trial (as will be discussed below). Unfortunately, performance status scales (e.g. Karnofsky) are general parameters that not only reflect neoplastic disease status but other parameters that may affect function such as pain. To date there is probably no ideal 'performance status' scale.

Polypharmacy

The practice of polypharmacy may confound the interpretation of some clinical trials. A study in 676 patients with advanced cancer found widespread use of adjuvant drugs for symptom control; the adjuvants most frequently used were phenothiazines (87%), corticosteroids (57%), night sedatives (54%) and antiemetics (44%). Daytime sedatives, non-steroidal anti-inflammatory drugs, antidepressants and anticonvulsants were also used.[58]

The concomitant use of drugs may affect the pharmacokinetics or pharmacodynamics of opioids. Drugs that induce hepatic mixed function oxidases, monoamine oxidase inhibitors and tricyclic antidepressants, used frequently in pain associated with cancer, may alter the metabolism of opioids.[32,59,60] However, the true influence of these drugs on opioid effects may be difficult to determine. Besides drug interactions, the side effects of adjuvant drugs may confound the side effects of the trial medications (e.g. sedation, confusion). It is important to control for specific pain adjuvant medications or ancillary treatments that may affect trial outcome (particularly in crossover designs where patient numbers may be smaller). An example of this is the double-blind crossover study comparing morphine to oxycodone reported by Kaslo and Vainio.[61]

Size of the study

In deciding the number of patients to include in a clinical study, researchers again face a dilemma. On the one hand they must consider the statistical implications of sample size. The risk of obtaining misleading results increases with small samples: at least 5% of small trials will yield differences significant at the 0.05 level by chance alone when there are no true differences in treatment efficacy.[41] Clearly, studies of cancer pain must be large enough to control for factors likely to confound results.

However, researchers must also consider how many potentially eligible patients can be entered in

the trial within a reasonable period of time. The absence of a critical mass of qualified researchers and of a central institution that would co-ordinate trials in this area are important constraints for patient accrual.[42] Another dimension is the selected nature of patients who may agree to take part in such studies. Consent rates of only 1 in 7 to about 1 in 12 or 13 eligible patients may be likely.[62]

Duration of the study

Researchers must likewise find a balance in terms of study duration. Treatment periods should be long enough so that patients will approach maximal response. Too short a period may not be adequate to demonstrate the efficacy or safety of the medication or delivery system tested. To illustrate this point, in a study in post-herpetic neuralgia, the effect of amitryptyline did not become manifest until week 6 of treatment. Any shorter treatment period would have given a negative result.[63]

On the other hand, too long a period of study may result in too few evaluable patients. For example, in a crossover study of cancer pain patients comparing heroin and morphine, only 21% of 699 patients who entered the trial did cross over, even though the initial period lasted less than 2 weeks.[64] Even in short-term studies, there is considerable uncertainty regarding how many patients will complete the study. In a crossover trial of controlled release morphine of 4 days' duration, Hanks *et al.*[46] reported a 50% dropout (out of 36 patients). One-half of this occurred before the trial actually started, in the 3 days between the day informed consent was obtained and the initiation of the study (patients no longer met inclusion criteria). Findings such as these illustrate that there may be an important number of patients who will not complete the study or for whom adequate data will not be collected for a variety of reasons. These include side effects during treatment, changes in disease status over the study period, factors that affect data collection, and ensuing death. Studying patients earlier in the natural history of their disease may limit dropout, even for short duration studies.

Factors difficult to control in ongoing clinical trials

Patient attrition

Loss of patients may be significant in long-term studies. In a study of 390 cancer patients given morphine during a 4-month period, 41 (10.5%) had interrupted treatment by day 20 of the study due to side effects or inefficacy.[65] Side effects may in some cases be due to metabolic deterioration (liver and kidney function, for example) which mandates that the patient be withdrawn from the study.

Acquisition of reliable data during clinical pain trials requires active participation from patients. This presents two types of problems. Reporting to treatment centres for evaluation may represent great effort on the part of many patients with progressively limited physical mobility. In a retrospective study of 90 cancer patients, Coyle *et al.*[25] found that at 4 weeks prior to death, 81% had Karnofsky performance scale ratings of 40 or below; 17% had a score of 50. Only 19% of patients were able to engage in some form of limited activity outside the home. Other data suggest that generalised weakness and physical and mental fatigue occur in more than two-thirds of patients with advanced cancer.[66]

Cognitive impairment may be frequent in terminal cancer patients. Using the Mini-Mental State Questionnaire, Bruera *et al.*[67] showed cognitive impairment in 39 out of 47 (83%) terminally ill patients measured, on average, 16 days before death. Massie *et al.*[68] reported that 11 out of 13 patients studied throughout the terminal stages of cancer experienced delirium. Bruera *et al.*[69] found that 23 out of 30 (77%) cancer patients (with no known brain metastases) who died at least 1 week after admission to hospital, developed impaired mental status (delirium in 16 and severe sedation in 7) on an average of 9 ± 6 days before death. This can make the assessment of pain intensity, analgesic response to treatment, or side effects difficult. Thus, as disease progresses, terminal cancer patients may be less able to respond to the demands of an interview, or other demands and restrictions imposed by the trial, compromising the completeness of data.

Clearly, patients would not be selected for participation in clinical trials at late stages of their illness. However, prediction of life expectancy in patients with advanced cancer is notoriously inaccurate.[70] In a study of 200 patients, 172 of whom had disseminated cancer, median survival time after referral to a pain clinic was 10 weeks (range 0.5–58 weeks).[18] Similar results were reported in a retrospective study of the epidemiology of terminal illness in 131 patients who experienced a terminal care period, defined as the condition where 'there is evidence of progressive malignancy, and in which therapy could not realistically be expected to prolong survival significantly.'[52] Ninety-seven per cent of the 131 patients experienced a period of terminal care which lasted on average 94

days, ranging from 1 to 1,320 days. Young age, better function and home-based care were associated with longer periods of terminal care. Psychosocial interventions have also been found to significantly increase survival in terminal cancer patients.[71]

Many patients entering clinical trials are likely to die or to deteriorate significantly enough during the trial to compromise data collection. An investigation of the use of oral morphine during a 4-month period gives some indication of losses that may be expected in long-term trials in terminal cancer. Out of an initial 390 patients, 22% had died by day 40, 58% by day 80, and only 73 (18.7%) lived to complete the study (47 patients did not complete the study for other causes).[65] Morris *et al.*[15] reported that the percentage (71%) of patients who were able to be interviewed initially in the National Hospice Study of pain declined to 36% within 14 days before death. Reuben and Mor[72] also reported substantial declines in the proportion of patients able to respond to interviews concerning nausea and vomiting as death approached. From an initial sample of 1,170 patients, only 63% were able to respond at about 21 days before death, and 46% at 1 week before death.

Even studies of short duration may experience significant patient losses, especially if they are small. A 5-day crossover trial to compare continuous subcutaneous and intravenous hydromorphine illustrates the contingencies that may arise with cancer patients. Data for five of the 20 patients who took part were not obtained for the following reasons: two patients died and one patient became encephalopathic; in a fourth patient the superior vena cava became obstructed, and in the last patient the intravenous cannula fell out and could not be reinserted.[73]

Patient compliance

All clinical studies are plagued by problems of non-compliance, but in pain studies with advanced cancer patients these problems are compounded. First, cancer patients with pain often have reservations about using opioids, due to fear of toxicity, addiction and mental confusion, which may restrict their use.[74] In spite of lack of evidence that long-term chronic use of opioids results in addiction,[17,75] myths regarding addiction and the stigma of using controlled substances prevail in patients' (and physicians') perceptions[17] and may compromise patients' compliance in clinical trials. In addition, patients may fail to comply because they may equate the use of narcotics with the finality of their life.[17]

Patients may also fail to report pain accurately if they believe that a new pain or the intensification of pain signals the spread of the disease.[74] Pain assessment may also be compromised by psychological disturbances such as raised levels of neuroticism, anxiety and fear, which augment pain perception.[38]

Assuming adequate instrumentation to assess pain, the procedure chosen for pain data collection (at predetermined times of the day, for example) may not be sensitive enough to detect swings in pain that may occur throughout the day. In the experience of some clinicians, some patients report more pain in the morning than during the rest of the day. On the other hand, the reverse may be true in other patients. Seeman and Lang[74] have found that some patients who cope with pain through socialising may have worse pain at night or during weekends.

Data on side effects

Accurate data regarding the occurrence of side effects, such as nausea and vomiting, with opioid therapy is complex in cancer patients owing to radiation therapy and chemotherapy which may be simultaneously administered and with which such effects are also associated.[62] Moreover, nausea and vomiting may be present in patients not receiving anti-neoplastic drugs and in patients with advanced cancer in association with metabolic disturbances, such as fluid and electrolyte abnormalities (e.g. hypercalcaemia, water intoxication, adrenocortical insufficiency); bowel obstruction; CNS or hepatic metastases; uraemia, local infections, septicaemia;[76] or autonomic dysfunction.[77]

Little is known about the relative contribution of different therapeutic or metabolic factors to nausea and vomiting in terminal cancer patients. However, a prospective study in 1,170 cancer patients during the last 2 months of life indicated that these symptoms are widespread.[72] Nausea and vomiting affected 62% of patients at some time during the 2-month period. Of 578 patients who completed all interviews, 21% reported these symptoms at all assessments. More than half of nauseated patients rated their symptoms as more severe than 'mild'. Patients with stomach and breast primary sites were significantly more likely, and patients with brain and lung primary sites less likely, to report nausea and vomiting. Women reported higher rates of nausea and vomiting than men, and these were unexplained by age, chemotherapy or tumour type (the relationship still held when breast cancer patients were excluded). Patients older than 65 years reported less nausea and vomiting than younger patients, but this was not associated with level of functioning. No attempt was made in this study to include the use of narcotic analgesics in the analyses. Nevertheless, the factors revealed by this study must

be considered in the assessment of nausea and vomiting attributed to administration of opioids in clinical trials.

Special efforts would also be needed to identify the relative contribution of an opioid to sedation in patients who are also receiving adjuvant medications that produce this side effect (e.g. tricyclic antidepressants). Similarly, it would be difficult to interpret to what extent abnormal laboratory parameters could be attributed to drug-induced toxicity of the tested drug, to adjuvant therapy, or to underlying progressive organ dysfunction.

Ancillary treatment

Psychological interventions to reduce anxiety, depression and pain have been shown to reduce cancer-associated pain[78] and to prolong life[71] in patients with metastatic breast cancer. Ancillary treatment of this kind, which may be useful for some patients, may change the nature of the study, introduce bias and interfere with the correct interpretation of results in clinical trials. Furthermore, restricting access to such ancillary treatment of terminal cancer patients already participating in a study would be unethical.

Conclusions and comments

The need for better and more efficient methods to treat pain in patients with advanced cancer is urgent. Clinical studies that are valid are needed to test the efficacy and safety of new analgesics or new ways of delivering analgesic medications. However, the multidimensional nature of pain in cancer patients tests to the maximum the resources available to researchers interested in advanced knowledge in this area.

The conflicting demands usually posed by randomised clinical trials[11] are intensified in cancer patients with pain. Validity is compromised by patients' baseline heterogeneity, instability and variability regarding pain. Strategies that may increase validity constrain the feasibility of the study and the generalisability of the results obtained. Constraints in eligibility criteria, difficult patient accrual, uncontrollable variables and uncertainties of follow up conspire against the validity, feasibility and generalisability of clinical trials in terminally ill cancer patients.

The challenges are multiple. Standard eligibility criteria required by many pharmaceutical firms may need to be re-evaluated in this patient population. In addition, the frequency of assessments may have to be limited in a patient group whose performance status and cognitive function may be borderline in order to improve compliance and limit patient attrition. Ideally, accruing patients at an earlier stage of the natural history of their disease, rather than in an advanced palliative situation, may improve numbers of evaluable patients. Stratification for pain syndromes or aetiologies, as well as a widely accepted staging system, may help deal with some of the issues of patient inhomogeneity. Study designs, such as cross-over designs of relatively short duration, need to consider the relatively small numbers of patients with potentially unstable disease. Finally, efforts need to be made to improve multicentre collaboration, with the development of more working groups, to accrue sufficient patient numbers within a reasonable period of time. Efforts must also be directed towards increasing the perception of the public, health workers and agencies concerned with medical research for the need and urgency of pain research in patients with advanced cancer. Increased funds allocated to the study of pain are vital to stimulate researchers and research institutions to concentrate more efforts in this direction.

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