Chapter 5. Future Research

Prevalence

Cancer-related Pain

Comprehensive, credible surveillance data describe the incidence and prevalence of cancer in the United States and survival rates for each major neoplastic disorder. The evidence that undertreated pain adds substantially to the disease burden of cancer is equally credible but less extensive and detailed. Limited cross-sectional data link tumor type and stage with pain quality or intensity (Caraceni, Portenoy, and the IASP Working Group, 1999), and there is no corresponding longitudinal, tumor-specific data on individual pain trajectories during treatment of cancer and cancer-related pain. Tumor- and population-specific data of this nature are needed if the natural history of cancer pain and its relief are to be understood with sufficient precision to advise individual patients and their families on the selection of pain control options. Data of this sort is available, for example, to facilitate informed choices by patients, families, and their care providers as to the likely progression, appearance of complications of, and risks and benefits of therapies for many prevalent conditions such as hypertension, heart disease, diabetes mellitus, infectious disease, and (as mentioned above) cancer itself.

Cancer-related Depression

There is much variance in the literature on reports of rates of both major depressive disorder and depressive symptoms in cancer patients. Even when standardized instruments are used, wide variance is seen. One recommendation would be to conduct prevalence studies that examine reasons for such variance and contributing factors for such differing rates. The timing of measurements of depressive symptoms appears to be important and may contribute to the variance. Since depression is more common in women in the general population, the effect of gender on depression in cancer patients needs to be more carefully studies. One goal may be to develop a statistical model that could predict the rate of depressive symptoms given the cancer, treatment, and demographics of the population.

The existing incidence studies of depression in patients with cancer all start at some time after the diagnosis of cancer. It is recommended that more studies start at the time of diagnosis, or even before if possible, to get better estimates of the incidence of depression once people are diagnosed with cancer. Both studies of incidence and prevalence should assess past histories of depression.

Research on the prevalence and incidence of depression in children with cancer is scarce and must be enlarged.

Cancer-related Fatigue

Studies of the prevalence of cancer-related fatigue are by no means comprehensive. Additional studies of fatigue prevalence in many types of cancer and many different clinical contexts are needed.

Data on fatigue prevalence are reported in studies on health-related quality of life, general studies of symptom prevalence, and from treatment trials in which fatigue is reported as a side effect. Extracting fatigue prevalence data from these sources could potentially provide a much more detailed and complete picture of the scope and impact of cancer-related fatigue. Methods

for comparing prevalence rates obtained using different assessment tools would need to be devised.

We were unable to identify studies that provided a longitudinal assessment of fatigue prevalence. All existing studies were confined to a brief period associated with treatment or a limited number of time points during the palliative phase or in cancer survivors. Thus, while data exists, for example, on the prevalence of fatigue in women with breast cancer during chemotherapy, radiation therapy, and in long-term follow-up, these studies use heterogeneous assessment techniques and do not provide insight into the time course of fatigue. There is a need for studies of the prevalence of fatigue over the entire course of treatment and follow up using uniform methods of assessment.

Assessment

Cancer-related Pain

The present sophistication of quality-of-life assessment, and documentation of relationships between pain, disability, and impairment, mandate that clinical trials of cancer pain control incorporate outcomes measures beyond mere pain intensity. Textbooks, guidelines and review articles on cancer pain all describe the need to perform a detailed history so as to assess the psychosocial and cultural frameworks and individual factors underlying pain experience and complaint. Such monographs further recount the importance of formulating whenever possible a mechanism-based pain diagnosis so as to guide therapy, the quantification of pain intensity as well as distress and impairment of quality of life and function associated with pain, and the reassessment of pain and distress across the continuum of care. Indeed, assessment of pain intensity and appropriate treatment are already clinical standards of the Joint Commission on Accreditation of Healthcare Organizations. To accomplish pain assessment and treatment related to clinical trials as well as clinical care in an increasingly diverse society creates a need for developmentally, culturally, and gender-appropriate instruments that are sensitive, reliable, and easy to administer. Instruments to assess health-related quality of life, particularly functional status, have been applied in recent years during cancer treatment trials. Analgesic trials for the most part have omitted such instruments, and those that incorporated them did so in a heterogeneous fashion. Because breakthrough pain contributes to overall pain morbidity in many patients, pain intensity itself is normally assessed in clinical practice not only at a single time but also across the course of illness and most importantly, during activity that includes movement. Uni-dimensional, “dip-stick” measures of pain intensity at rest, repeated a few times during a short observation interval and often after only a single dose of medication, must be supplanted by more clinically relevant and comprehensive pain assessment during clinical trials.

Important information to strengthen interpretation of the results of clinical trials is at present mostly lacking. Such information, to permit responder or non-responder subgroup analyses, includes genetic and genders characteristics, medical comorbidity and concurrent treatments, as well as other individual features such as ethnicity and culture.

Because side effects of therapy often limit doses of analgesic agents employed, and contribute to global morbidity associated with cancer pain, the prospective assessment of side effects should be accomplished with the same care as has been bestowed upon assessment of analgesia. To do so will require development and validation of age and culture-appropriate scales for individual side effects that may appear during therapy.

Cancer-related Depression

There are many screening and assessment instruments currently available for depression in cancer patients. Researchers can choose instruments based on ease of use versus the instrument performance. The performance of brief instruments that appear to have promising predictive value, such as the one-item, "Are you depressed?," require further study and replication. The development of short instruments that assess all three symptoms (depression, pain, and fatigue) could be one possible area of future research.

Although some of these instruments are currently being used in clinical practices, there are currently no published studies of their effect on outcome. Outcome research, both psychological and medial, needs to be done using the instruments as "lab tests."

More research needs to be done on the assessment of depression in children with cancer.

Cancer-related Fatigue

Further research is needed on methods for the clinical evaluation of fatigue. A useful strategy would involve studies to validate the screening and assessment algorithms recommended in the NCCN practice guidelines on cancer-related fatigue. These would include studies on the utility of brief fatigue screening tools such as visual or verbal analogue scales in different clinical settings, and on the clinical application of more elaborate assessment instruments. Further research is also needed on the prevalence of treatable factors contributing to fatigue, and the reversibility of fatigue based on the treatment of these underlying factors.

In the research context, there should be a continued reliance on assessment instruments that are well characterized in terms of their validity, consistency and reliability. Clinical interpretation of the outcomes of these measures still remains problematic. Further comparisons are needed between data on fatigue in cancer patients and normative data from control groups.

Given the large number of instruments used to assess fatigue, methods to compare results from studies using different instruments are needed. Researchers in this field should consider developing consensus criteria for the assessment of fatigue for use in future studies.

Treatment

Cancer-related Pain

This is an exciting time in translational research on cancer-related pain, because preclinical research has generated novel insights into distinctive mechanisms through which tumors produce pain. Increased understanding of the pathogenesis of cancer-related pain (as well as other symptoms such as depression and fatigue) may foster therapies that are increasingly targeted, i.e., mechanism-based. At present, however, in nearly every respect (number of trials, sample size, representative study populations, and study design), the quality of the scientific evidence on cancer pain treatment compares unfavorably with that for cancer treatment. Cancer treatment trials for the most part exemplify mechanism-based clinical research. Leading investigators in the area of cancer pain relief trials have repeatedly called for improving the quality of trials in this area. This goal cannot be achieved merely by incorporating standardized pain assessment and health-related quality-of-life measurements into cancer treatment trials. Although such a strategy is laudable, data so gathered cannot be generalized to the treatment of pain during intervals of stable disease, or to patients who are in remission but who continue to experience residual pain. Carefully designed trials with pain or pain relief as a primary outcome are required in diverse populations with well-defined disease. These groups include patients with stable

disease, others with treatment-induced, incident, or breakthrough pain, and those with specific pain syndromes (such as postmastectomy syndrome) during disease remission.

Standards for cancer pain treatment trials must adhere to those for clinical trials in general, as expected by editors of most leading medical journals. Trials of cancer pain relief should enroll more patients and follow them longer than has generally been customary in the past; apply blinding and active placebos, when appropriate, or uniform control treatments otherwise; employ adequate between-arm washout intervals and consider advancing disease state in crossover trials; and assess side effects, pain mechanisms, and rest, incident, or breakthrough pain in a standardized, combinable fashion. To these criteria must be added the need to study gender, race, age, ethnicity and culture with greater precision than in the past, to avoid overgeneralization of results. Categorizing patients by tumor type and stage, and by mechanism of pain, with inclusion criteria that yield homogeneous groups within individual studies, appears to offer the best chance of translating preclinical advances into improved clinical analgesia. Pilot studies that indicate gender and ethnic differences in analgesic pharmacokinetics and pharmacodynamics merit larger scale follow-up. Small-scale, short-term randomized controlled trials that establish treatment efficacy for purposes of Food and Drug Administration approval are not designed to prove effectiveness in larger scale, long-term applications in the treatment of cancer pain relief. To meet this need, outcomes research can provide valuable data that are not feasible to acquire through controlled trials.

Just as combination chemotherapy is employed to treat many forms of malignancy, the practice of analgesia commonly involves drug co-administration. Methods are needed to synthesize published evidence on drug interactions and to apply and extend existing methods (now employed in acute pain studies) to characterize such interactions during long-term cancer pain treatment. Related to this area is the important issue of developing clinical evidence on optimal strategies for the sequence of drug therapies employed for cancer pain control (that is, the WHO model or other treatment algorithms), and the optimal means to combine drug and non-drug therapies. Trials to address these issues, like those to evaluate one component of a multidrug antitumor regimen, are effort intensive and may require large numbers of subjects per treatment arm.

Data on individual variation in preferences for, responses to, and costs of drug and non-drug interventions are limited. For example, the spinal route of analgesia is widely employed but much remains to be learned about optimal patient selection, the comparative efficacy of spinal drug infusion versus systemic drug administration, and the selection of initial or secondary agents or combinations. Drug interactions during long-term cancer pain treatment require clarification. A host of complementary therapies are now employed, but with little rigorous testing of their efficacy. It is unclear whether a mechanism-based approach to diagnosing and relieving each component of pain in an individual is more effective than an empiric regimen in which each patient’s treatment is based upon pain intensity alone. Another key unanswered question is how to optimally combine drug with non-drug therapies given that the latter are safe and inexpensive. Despite the importance of pediatric cancer pain control practically no analgesic drug trials focus on children.

Cancer-related Depression

Psychopharmacologic, psychosocial, and alternative interventions offer some benefit on treatment for depressive symptoms with cancer patients. Research needs to be done to support current clinical practices in the prescribing of medications for depression in cancer patients.

Because antidepressant medications have been shown to be effective, the newer antidepressants, especially the atypical ones, should be studied in this population. There should also be more trials of the use of antidepressants for the prevention of depressive symptoms in patients with cancer.

Hundreds of studies exist on psychosocial interventions for cancer patients and depression, but a meta-analysis specifically of treatment studies on depressed patients remains to be done. This will probably change the effect sizes estimated in the meta-analyses that included large numbers of prevention trials and may better differentiate between the effectiveness of types of psychosocial interventions.

To evaluate their efficacy, controlled trials on alternative therapies for depression in cancer patients should be done. Studies on the treatment of depression in children with cancer are needed.

Cancer-related Fatigue

The absence of treatment options for cancer-related fatigue reflects a lack of understanding of its fundamental physiology and the very small number of controlled clinical trials that have addressed this problem. Further basic research is needed, including the development of animal models to study the role of cytokines, nutritional factors, muscle wasting, and other potential contributors to fatigue. Studies correlating such factors with fatigue in cancer patients are also needed in order to develop rational hypotheses for treatment trials.

Several promising strategies for treatment of fatigue have been identified based on preliminary clinical trials or clinical experience. These strategies require further investigation in randomized controlled trials. Among the more promising treatment approaches are exercise programs, psychosocial interventions (with a particular focus on the detection and treatment of depressive symptoms), and stimulant medications. Research on fatigue in other contexts may provide leads for effective therapies in cancer patients. For example, Breitbart, Rosenfeld, Kaim, et al. (2001) recently reported improvement in fatigue associated with the psychostimulants methylphenidate and pemoline in a randomized, placebo-controlled trial in patients with HIV disease.

Other potential treatment approaches that warrant preliminary laboratory investigations and/or pilot trials include hormonal treatments such as human growth hormone, melatonin, and androgens, as well as anti-inflammatory medications, and dietary interventions.

Future clinical trials for cancer-related fatigue should use appropriate study designs, including prospectively defined endpoints. They should be appropriately powered to detect differences in the endpoints of interest. Strategies are needed to identify and eliminate barriers to effective diagnosis and treatment of fatigue and other cancer symptoms, and to enhance accrual to studies of these symptoms.

Concurrency and Interactions between Pain, Depression, and Fatigue

Clinical impressions and a small amount of observational data suggest that the three cancer-related comorbidities of pain, depression and fatigue are often concurrent and reinforce each other in their corrosive effect upon quality of life. For example, immobility due to movement-related pain may result in deconditioning as well as poor sleep, that in turn augments depression and fatigue; or, depression and fatigue may render a patient less compliant with an analgesic

regimen that requires remembering multiple medications to be taken at different times, and kept in a site in the patient's home different from where the patient spends most time (e.g., the bedroom). The organization of the present State-of-the-Science Conference that focuses upon this symptom triad reflects widespread opinion that each of these elements often co-exists and interacts with the other. Definition of the concurrency of these interactions within distinct subjects and contexts, the assessment and quantification of such interactions, and analysis of how treatment of one or more elements influences the others are all potentially important topics for future research. Such research, conducted in patients who may be very ill, have fluctuating physical function, mental status and mood, and shifting patterns of pain is often challenging. Nonetheless, the clinical research community concerned with improving symptom control in patients with cancer has already shown itself capable of surmounting these and other challenges in providing a strong evidentiary base upon which to base further research and daily clinical care.