Chapter 4. Conclusions

Prevalence

Cancer-related Pain

Pain is an important component of the already considerable disease burden of cancer. Minorities, women, and the elderly are particularly at risk for cancer-related pain, and this observation possibly reflects both underassessment and undertreatment. Nearly all epidemiological studies that contain population-based estimates of the prevalence and severity of cancer pain report few details concerning specific mechanisms of cancer pain, nor do they track pain and other symptoms longitudinally across time; however, credible survey information is emerging that suggests the prevalence of pain and other symptoms is related to the type of cancer (though not related to information such as grade or stage). The total number of patients surveyed in published reports of the prevalence and severity of cancer-related pain, as well as in methodologically sound trials of cancer pain relief, is a minor fraction of those receiving care—much lower than for nearly all other high-impact, costly conditions. There remains an incomplete picture of variations in cancer pain prevalence, severity, and course with respect to: patient factors (age, gender, ethnicity, race, culture); disease characteristics (type, grade, stage as well as other features such as genotypic or phenotypic classification); the setting in which care is provided (provider attributes and professional qualifications, location and nature of healthcare practice); and specific treatments directed toward the underlying disease and its associated pain.

Cancer-related Depression

Major depressive disorder and depressive symptoms occur frequently in patients with cancer. Despite using standardized measures, there is a wide range of reported incidence and prevalence. From our review of the literature, the prevalence rates appear to be between 10 to 25 percent for major depressive disorder and a similar range for clinically significant depressive symptoms regardless of psychiatric diagnosis. Given that the estimated point prevalence of major depressive disorder is 2.2 percent in the general population, these rates in cancer patients may be at least four times greater.

Despite using standardized measures, there is a wide range of reported incidence and prevalence. This range may be the result of several factors that include the timing of the assessment, concurrent treatment, medical morbidity and pain, and age. Cancer patients are a heterogeneous population with different sociodemographics, cancer types, treatments, and responses to treatment. More accurate estimates might be obtained in studying the rates in more homogeneous sub-groups.

Reports on the incidence of depressive symptoms are limited to prospective studies of patients receiving certain cancer treatments. Reports of incidence range widely from about 2 to 17 percent during the time frame of the studies. Although it is difficult to generalize these results to all cancer patients, the incidence appears to be somewhere between 2 and 7 percent per year. However, these studies, like the prevalence studies, face the same difficulties of heterogeneous populations, and there are too few naturalistic studies that follow patients from the time of diagnosis conducting serial depressive assessments. Despite the lack of high quality data, it appears that the incidence of depression in cancer patients is much higher than the general population's yearly aggregate incidences: 0.25 to 0.6 percent for women and 0.08 to 0.2 percent for men.

Cancer-related Fatigue

Estimations of fatigue prevalence have been performed in many settings but the data is by no means comprehensive. Our search identified 27 reports on fatigue prevalence. Thirteen studies included patients with a variety of cancers, five studies addressed breast cancer at various stages and during various treatments, and four focused on lung cancer and two on prostate cancer. Many types of cancer were not specifically addressed. A more complete picture of cancer-related fatigue could be obtained by extracting fatigue prevalence data from HQL and general symptom studies, and from clinical trials in which fatigue is reported as a side effect of treatment.

A very broad range of prevalence rates has been reported. Prevalence rates ranged from 4 percent in breast cancer prior to starting chemotherapy and 8 percent in prostate cancer prior to radiation therapy (Jacobsen, Hann, Azzarello, et al., 1999; Monga, Kerrigan, Thornby, et al., 1999), to 91 percent in breast cancer patients after surgery and chemotherapy and before bone marrow transplantation (Gaston-Johansson, Fall-Dickson, Bakos, et al., 1999). Findings of significant concern were the prevalence rates of fatigue in cancer survivors: 26 percent in Hodgkin's disease survivors (Loge, Abrahamsen, Ekeberg, et al., 1999); 35 to 56 percent in breast cancer survivors (Bower, Ganz, Desmond, et al., 2000; Okuyama, Akechi, Kugaya, et al, 2000); and 48 percent in a cohort treated for cancers (Servaes, van der Werf, Prins, et al., 2000).

Comparisons of the prevalence rates in these studies are problematic, however, since each study used different criteria for defining the presence or absence of fatigue and its severity. A few studies used criteria for fatigue that were based on normative data from control populations (Stone, Hardy, Broadley, et al., 1999; Bower, Ganz, Desmond, et al., 2000). In many studies, however, the criteria for fatigue were arbitrary.

Population-based surveys of fatigue prevalence (Vogelzang, Breitbart, Cella, et al., 1997; Cella, Davis, Breitbart, et al., 2000) represent an advance since they potentially avoid the selection bias inherent in small cohort studies, although other bias may be introduced by the fact that only a minority of potential subjects were contacted. The primary purpose of the study by Cella, Davis, Breitbart, et al. (2001) was to evaluate proposed ICD-10 criteria for cancer-related fatigue, which, if adopted, would allow comparison of data from a wide range of sources.

The period over which the prevalence of fatigue was assessed in any group of patients was short, generally confined to the period of treatment and immediately after, or one time point in studies of survivors. No studies used a uniform methodology to track the time course of fatigue longitudinally. Few studies on the prevalence of fatigue included data on factors that might contribute to fatigue (such as anemia, infections, etc.), or attempted to determine to what extent fatigue was due to treatment, disease, or other factors.

Assessment

Cancer-related Pain

One hundred eighty-four unique trials were retrieved for the prior evidence report, plus an additional 34 in the updated search, for a total of 218 trials. In these trials, a total of 125 different outcome measures were employed. Many were similar to each other but not directly combinable, e.g., four-point and five-point pain intensity scales. The most frequently employed scales were of pain intensity: the 0-100 VAS (58 uses), a 10 cm VAS (44 uses), and five-point (26 uses) or four-point (24 uses) pain intensity scales. Of the 21 instruments that were employed five or more times in the pooled retrieved studies, four were numerical measurements of pain intensity and one was an integrated pain intensity score, three were pain relief scales, two were peak or summed pain intensity differences between treatments, two were global evaluations or global

efficacy of intervention scales, and one was the McGill-Melzack pain questionnaire. Only one of the 21 most frequently applied instruments (a four-point scale) appraised side effects (5 uses); analgesic consumption was assessed 21 times.

The need for detailed assessment conducted within a psychosocial framework is addressed in virtually all guidelines or monographs on cancer pain management. A voluminous literature exists that describes the multidimensional, experiential nature of cancer pain and links poor control of cancer pain to impaired quality of life, including functionality. Expectations for detailed, multidimensional assessment of cancer pain, including quality of life assessment, during cancer care contrast with minimalist assessments of pain intensity presented during relatively brief observation intervals reported in nearly all of the retrieved trials. Side effects limit analgesic dosage and hence impede pain control in many patients, yet only one of the 16 most widely employed outcomes measures addresses the issue of side effects; that one is a coarse, four-point measure.

Cancer-related Depression

The clinical interview, using DSM criteria, is the standard of care for diagnosing major depressive disorder and other depressive syndromes in people with cancer.

Because depression may go undetected and untreated in oncology practices, the importance of screening tools and rapid assessments has been emphasized. Many self-report assessments are available that could be completed by patients before visits in clinic waiting rooms. These assessments range from circling answers to series of questions to The Distress Thermometer, a modified visual analogue scale that is presented in the NCCN guidelines for the treatment of psychosocial distress. Available data on the sensitivity, specificity, predictive values, and cross-correlations are presented in the evidence-based table.

Although these assessment tools may have been validated in studies, there is currently no evidence on how widely they are used clinically or to suggest that they affect clinical care and outcomes.

Cancer-related Fatigue

The literature on fatigue assessment focuses on tools that are used in research studies, and to a much lesser extent on methods of assessment for clinical use. The NCCN practice guidelines on cancer-related fatigue recommended the use of simple 0-10 numerical self-report scales or verbal scales (e.g., mild, moderate or severe) to assess the severity of fatigue in practice settings. This recommendation is based on a study by Piper, Dodd, Ream, et al. (1999) correlating self-report scores on a 0-10 scale of fatigue with the Physical Functioning Subscale of the Medical Outcomes Study Short Form 36 (SF-36). They found a significant impairment in physical function on the SF-36 when fatigue scores were ≥ 7. If moderate or severe fatigue is reported, the NCCN panel then recommended a focused history and physical examination and evaluation of the pattern of fatigue, associated symptoms, and interference with normal functioning. Five potential causes should be addressed because they are common and potentially reversible: pain, emotional distress, sleep disturbance, anemia, and hypothyroidism. A review of medications was not included in this initial evaluation although in practice this is certainly done. If no etiology of fatigue is identified, the NCCN panel recommended a more comprehensive evaluation, education and counseling, and consideration of a variety of strategies to reduce fatigue. Although this approach is not based on controlled clinical trials validating its effectiveness, it is intuitively

reasonable. It would be useful to know the extent to which causes of fatigue can be identified and reversed using this algorithm.

In the context of clinical research, assessment of fatigue involves the use of patient self-assessment tools of varying levels of complexity. Most studies in the last several years have used instruments that assess multiple dimensions of fatigue and have been tested for validity, consistency, and reliability. Issues still remain in terms of the clinical interpretation of the scores obtained on these instruments, and the comparison of fatigue measurements obtained using different instruments.

Treatment

Cancer-related Pain

As reported in the prior evidence report, the number of randomized controlled trials to evaluate analgesic interventions for cancer pain is approximately one percent of the total of initial titles retrieved. The heterogeneity of existing trials precludes meta-analysis to answer most clinically relevant questions. For example, the trials do not disclose differences between the relative efficacy of opioids and nonsteroidal antiinflammatory drugs (NSAIDs) administered by various routes to patients with mild, moderate or severe cancer pain. There is evidence of an opioid dose-sparing effect from co-administration of an NSAID but no consistent reduction in side effects from doing so. There is little evidence for significant differences in analgesic efficacy between NSAIDs (only one trial out of 18 reported this outcome). The studies comparing different NSAIDs could not be combined in a meta-analysis due to between-study heterogeneity in the outcomes assessed, drug doses and schedules compared, and study duration. Trials that compare the efficacy of NSAIDs versus “weak” opioids (i.e., opioids commonly prescribed for mild to moderate pain) reveal no difference in analgesic efficacy between these two classes of agents, even when the latter are co-administered with the same NSAID tested in the other study arm. These trials enroll relatively small numbers of patients and are of relatively short duration. A single randomized controlled trial of breakthrough pain treatment demonstrated the superiority of oral transmucosal fentanyl citrate to placebo. We found no randomized controlled trials addressing analgesic efficacy and safety of NSAIDs selective for the cyclooxygenase-2 isoenzyme in treating cancer pain.

Published trials exploring different routes of administration for NSAID or opioid drug classes show no difference in analgesic efficacy between oral or rectal routes of delivery of each class of drug. Limited data from trials show no benefit from a purely analgesic standpoint of parenteral (intramuscular or intravenous) administration over enteral administration. Failure to prove overall superiority of one route over another does not diminish the value of a particular route in a specific clinical situation (for example, the use of suppositories or transdermal administration in the presence of dysphagia). Insufficient information exists to permit comment upon differences in patient preference for specific routes and administration, or acceptability of side effects. There was no evidence to indicate improved analgesia with controlled-release oral formulations versus immediate-release formulations or transdermal delivery. The benefit of less frequent doses upon patient compliance is a possible advantage of controlled-release formulations.

Trials of biphosphonate therapy are heterogeneous with respect to inclusion criteria, concomitant medical and radiotherapeutic treatments, disease categories, dosage regimens, choice of agent, and duration of follow-up. Differences in pain assessment methods are also considerable, ranging from analgesic consumption to a “requirement” for palliative radiation therapy. However, many studies showed a positive effect, some showed no effect, and no study

showed a detrimental effect of biphosphonate therapy on skeletal symptoms of metastatic disease or myeloma. Positive effects were less evident in patients who received concurrent hormones or chemotherapy that might by themselves have a favorable effect on bone symptoms. The evidence in aggregate suggests that biphosphonates are effective in reducing bone pain in patients with cancer, although this benefit may be less marked when such therapy is combined with other tumor-directed therapy. The radionuclide strontium-89 was more effective than placebo (inactive strontium), and equally effective as external radiation.

The literature on the effects of various chemotherapeutic and hormone therapy regimens on pain is also quite heterogeneous, with differing inclusion criteria and therapeutic regimens. Analgesic consumption is reported in a minority of these studies. In only one chemotherapy trial, and in no hormonal therapy trial, did pain outcomes differ significantly between treatment arms.

Eighteen trials compared fractional dosing schedules of external radiotherapy for pain from bony metastases. No trial found more than a transient difference in pain between fractionation schedules, although external radiation as a whole is effective in decreasing pain. Meta-analysis was precluded by heterogeneity of the dosing schedules, variability in the anatomic sites and fields treated, and outcomes assessed. Short courses (even single doses) of palliative treatment with higher doses appear to produce results similar to those of longer courses that deliver a lower dose per treatment. The minimal total dose of radiation to provide pain relief has not yet been determined. A possible detrimental effect upon quality of life due to transient skin irritation and discoloration at the site of post-mastectomy chest radiation was reported in one study (Whelan, Levine, Julian, et al., 2000).

The number of studies of physical or psychological treatments to decrease cancer-related pain is small, and variability of the specific intervention and type of pain addressed precludes any broad conclusions. Studies of education evaluated different interventions in patients, medical staff, and the community at large. Studies of hypnosis in the pediatric and adult age groups indicate benefit for procedural and mucositis-related pain. Cognitive behavioral treatments may also be helpful. More studies are needed, with larger numbers of patients and control groups.

Sufficient randomized controlled trials on neurolytic celiac plexus block (NCPB) for pain relief in pancreatic and other visceral cancers were identified to indicate the efficacy of this modality. NCPB lowered pain scores or produced a prolonged dosage-sparing effect upon analgesic drug requirement. The scarcity of randomized or controlled trials on the efficacy of spinally administered opioids or other agents led us to retrieve nonrandomized reports in an effort to estimate the efficacy of this modality. These additional reports, although positive, were case series without control groups and hence yielded no data on relative efficacy of the spinal versus systemic route of drug administration. Similarly, the efficacies of ablative neurosurgical interventions such as cordotomy or rhizotomy were addressed only in case series. There were no trials that addressed the efficacy of acupuncture.

Cancer-related Depression

The current evidence shows that interventions are beneficial for depressive symptoms in cancer patients. There appears to be a clear benefit of psychosocial interventions, although the magnitude of the effect size seems to be in the mild to moderate range. Because of the hundreds of studies on psychosocial interventions in cancer patients, we limited our review to published meta-analyses of these studies. However, in limiting our review in this way, the contribution of effects from preventive studies and depression treatment studies could not be separated. The effects of psychosocial interventions may vary in these two different kinds of studies.

Although not all pharmacologic studies showed benefit for depression in cancer patients, all studies that used antidepressants and conformed to usual practices for antidepressant trials did show benefit. Since antidepressants typically can take four to six weeks for their full effect, studies of antidepressants under five weeks tended to show less benefit. Currently, there is efficacy data for selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. Another antidepressant that showed benefit, mianserin, is an atypical antidepressant not available in the United States. Although trazodone, an atypical antidepressant, showed some benefit in treating depressive symptoms, it is not commonly used as an antidepressant because it often causes sedation at therapeutic doses.

No controlled studies on alternative treatments for depression in cancer patients were identified.

Cancer-related Fatigue

Ten randomized, controlled trials were identified that assess interventions for cancer-related fatigue. Four involved psychosocial interventions (support groups, psychotherapy, relaxation therapy, and a comprehensive coping strategy program). Three clinical trials evaluated the impact of exercise on fatigue. One trial involved massage therapy and one evaluated a "bedside wellness system" using virtual reality technology. There was only one trial of pharmacotherapy (epoetin alfa for fatigue related to anemia in patients receiving chemotherapy). Some of the concerns regarding the methodology of these studies are addressed in the results section. Endpoints were often poorly defined and sample size calculations absent. It is probable that many of these studies were underpowered to detect the outcome of interest. Although several studies reported statistically significant associations between the intervention being tested and various outcomes, the absence of prospectively defined endpoints renders these results difficult to interpret.

The studies by Mock, Hassey Dow, Meares, et al. (1997) provides evidence that exercise may be helpful in reducing or preventing fatigue in patients receiving radiation therapy for early stage breast cancer. The beneficial effects of exercise are less clear in other contexts such as peripheral blood stem cell transplantation (Dimeo, Stieglitz, Novelli-Fischer, et al., 1999). Nonetheless, this is certainly an approach that warrants further investigation.

The randomized, placebo-controlled, double-blind trial by Littlewood, Bajetta, Nortier, et al. (2001) suggests a substantial benefit associated with epoetin alfa in terms of quality of life, fatigue, and hematologic parameters in anemic patients undergoing chemotherapy. The findings of this study are supported by large, non-randomized trials.