

INTRODUCTORY LECTURES

Clinical Aspects of Pharmacogenetics of Pain and Co-Morbidities of Emotional Distress

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Abstract

The majority of patients treated for cancer will have pain at some point in their journey. It will be due to the disease (e.g. bone metastasis, fracture, organ invasion) or from iatrogenic causes (chemotherapy, surgery or radiation). A large number of patients will also have depression. Since pain and depression share common biological pathways and even neuro-transmitters it is not surprising that a comorbidity of pain is depression. It has already been reported that patients in severe pain are 4 times less likely to respond to therapy for depression. In recent years, especially in the era of molecular biology and post-genomic a wealth of data in the arena of pharmacogenetics/genomics has shed more light on cancer related symptoms such as pain and related them to the cytokine pathways, especially the interleukins and tumor necrosis factor (TNF). When we remember that the synonym for TNF is 'cachectin' it is no wonder patients feel awful when there is active disease and the body trying to mount a response. Neuroendocrine, immunomodulatory and inflammatory pathways are likely important in the pathophysiology of pain and depression. These realizations are in addition to a greater understanding of afferent pathways for pain perception, of the multiple opioid receptors, the effects of hormones and catechol metabolism and other transmitters. Moreover we already have a more complete understanding of drug metabolism, especially of the opioids, the back bone of all pain treatment. There are a number of single nucleotide polymorphisms (SNPs) in the genes important for drug metabolism such as CYP2D6, a cytochrome responsible for about 25% of all drugs. There are about 90 variants already reported and rapid and slow metabolizers need very different doses of codeine or morphine. We are entering an era of having the capability to develop personalized treatment for our patients' nociceptive pain, neuropathic pain and depression. The convergence of new knowledge in the molecular biology and pharmacogenetic era should allow us to treat our patients' suffering with a resultant increased quality of life even while we strive to cure them of their malignancy.

Keywords: Cancer pain - co-morbidity - depression - drug metabolism - drug choice

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Introduction

There are multiple definitions for pain found on the internet. Two simple, brief notations are: A) *a symptom of some physical hurt or disorder* and B) *emotional distress; that is a fundamental feeling that people try to avoid* are crucial to realizing that pain and depression will often co-exist. Although most assume that somatic pain can cause depression, we also need to remember that depression (defined as sad feelings of gloom and inadequacy) will exist in the absence of pain. While it is argued that co-existence does not prove causation or interdependence, but simply an association (Laird et al., 2009), in the cancer literature and my own personal experience spanning three decades it would seem that pain is at least partially a causation of depression. The successful treatment of pain can decrease or even eliminate depression and in a recent study, pain was a strong predictor of depression and patients with severe pain were four times

less likely to respond to depression treatment (Blair et al., 2004). This is important as the prevalence of depression and pain, especially in patients with advanced disease has been reported to be in the 50-80% range.

Maintaining a high quality of life with respect to somatic complaints is even more important when it is realized, that especially in the cancer literature, the pharmacological treatment of depression is difficult. As recently stated "*There is still a lack of pharmacological treatment algorithm for major depressive disorder in patients with advanced cancer.....There might be two ways to better understand the paradoxical lack of efficacy of anti-depressants in oncology. First cancer patients would not have same reactivity and sensitivity to pharmacological treatment.... and second...there might be overlap and confusion between somatic factors (pain and fatigue) inducing psychological distress....*" (Reich, 2008). In this regard and in retrospect, if I were to have broadened the scope of this brief discussion, I would have

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changed the title somewhat to be inclusive of fatigue, as a reminder that it is another major symptom in patients with cancer. In fact fatigue is one of the most common chief complaints in an oncology clinic whether it is caused by the underlying disease (see Reyes-Gibby et al., 2008 for general review) or, as we have previously discussed, that pain and general suffering (e.g. signs and symptoms including nausea, malaise, and anemia) are very often iatrogenic (Kamen and Saletsky, 2000).

There are numerous original reports and recent reviews discussing the co-morbidities of pain and depression. Point of fact is that simply searching “pain and depression and cancer” yields approximately 1,400 citations and only “pain and depression” yields more than 16,000. Bair et al (2003), Reich (2008), Reyes-Gibby et al (2008) and Laird et al (2009) are recent reviews that I found very informative in synthesizing this overview.

Acute pain perception (nociception) is often severe but limited and will usually respond to opioids. Neuropathic pain, often instigated by an injury may persist for a long time after the injury has healed. It remains chronic, responds less well to opioids and is more difficult to treat. While acute pain can serve as a warning to us that damage has been done and that we need to react (e.g. stepping on a nail) in a protective manner, neuropathic pain is more akin to a malfunctioning of the alarm system and as noted, more difficult to treat. In either case, since studies of both neuro-transmitters and imaging studies of the cerebral cortex show a commonality of pain and depression, it stands to reason that elimination of pain should often help to ameliorate severity of depression.

The somatic problems of pain, asthenia, general malaise/fatigue of cancer are at least in part due to the body’s response (i.e. cytokines and hormones) as well as the tumor causing local and systemic reactions by releasing pro-inflammatory cytokines, and simply mass effects (e.g. brain and bone metastases). As we have accepted that depression can be associated with these somatic issues, it is logical to conclude that overall quality of life for our patients, both physically and psychologically can be improved through control of somatic issues, perhaps with anti-inflammatory agents capable of treating cause, not just blocking perception as the opioids do. Finally, a patient with advanced cancer, even having no somatic disease caused by the cancer may still have depressive problems simply knowing that their time is limited, but this issue will not be discussed here.

Below I will broadly discuss the pathophysiology-biochemistry of pain as caused by a tumor and/or the host response as well as noting some of the more well appreciated ADME (absorption, distribution, metabolism and excretion) phenomena of pharmacokinetics. These two issues are important as we think about treating our patients. Given the difficulty of isolating pure depression as well as the problem in treating it as noted above and space limitations, the emphasis here will be about pain and how when we look at cancer as a “state of being” or at least a complex tissue, that new alternatives for treating a patient’s symptoms emerge. Reviews of the management depression are cited (Bair et al., 2003; Reich, 2008; Laird et al., 2009)

The Host (a euphemistic term for patient) - Tumor Relationship

is clearly a source of some cancer related symptoms. Cancer is a state in which a malignant cell usurps or bypasses the usual humoral or internal controls, that is the regulatory pathways governing proliferation. The end result is abnormal growth and metastatic spread. There are at least two critical issues here.

First, the body’s own defense mechanisms that have evolved for defeating intruders such as infectious agents may react to the presence of a malignant cell. An appropriately intense inflammatory response or immune response may result in cancer control, indeed immunotherapy, whether active or passive remains a major area of clinical and basic research. Humoral responses by macrophages, dendritic cells and T-effector cells will often be mediated or initiated by the production of potent cytokines as immune and inflammatory modulators. The significance of a robust systemic reaction to a tumor may be analogous of the reaction to a bacteremia. If our defense mechanisms respond appropriately to a bacteria producing endotoxin we are cured, if the response is too exuberant, endotoxic shock or disseminated intravascular coagulation may occur. We only have to remember the side effects of exogenously administered interferons and interleukins or that tumor necrosis factor was initially identified and named cachectin because of its systemic effects to realize that somatic complaints can be related to the body’s reaction to a tumor e.g. as in a patient with severe B symptoms such as fever, asthenia, pruritus with or without rash and night sweats.

Second, the malignant cell will take control/advantage of the local environment that will result in it evading the immune system and stimulating vascularization so that it may grow locally as well as spread systemically. Specifically, the cancer cell itself can elaborate immune suppressive molecules such as transforming growth factor α and cytokines that block the normal defenses and other molecules that are pro-angiogenic. Cytokines are pleiotropic depending on location, concentration and other molecules in the environment. Over abundance of some such as IL 6 are associated with poor prognosis as well as pain as seen in auto-immune diseases like arthritis. There are a number of polymorphisms altering normal cytokine function that are associated with somatic disease and likely even psychological disturbances as very recently reviewed (Reyes-Gibby et al., 2008). The implications here relate to both the control of cancer related symptoms as well to potential control of the tumor. From a treatment view, recognition of an imbalance of cytokines and the robust inflammatory process allows the suggestion of using well tolerated drugs such as cyclooxygenase inhibitors or other drugs such as soluble receptors for TNF to eliminate somatic complaints or even control the tumor. Perhaps more specifically, an antibody against IL 6 is also being evaluated as noted by Reyes-Gibby et al (2008). Using more traditional anti-cancer drugs but scheduled in a more repetitive manner and dosed much lower than used in conventional regimens (i.e. metronomic chemotherapy) has also shown promise. Low dose, daily

cyclophosphamide combined with daily celecoxib or methotrexate given twice a week have shown activity in prostate and breast cancer respectively (Glode et al., 2003; Wong et al., 2010). The drug doses are those that would be used in the setting of auto-immune disease or graft versus host, not the typical high dose therapy according to the usual paradigm of DLTs and MTDs (dose limiting toxicity and maximally tolerated doses). These lower doses are anti-inflammatory, anti-angiogenic and immune modulatory thus providing some control of tumor metastases and growth as well as providing a non-opioid treatment for cancer related symptoms! More studies need to be done, but if we can balance the control of the inflammatory process and cytokine production and properly sway the immune system towards effector cells, rather than self recognition we may achieve control of disease and symptoms. But we always need to be wary of tipping the balance in the wrong direction.

Pharmacokinetics and Dynamics of Treating Patients Pain

Opioids, natural, semisynthetic or synthetic remain the essential ingredient in the armamentarium for treating cancer related pain. Morphine remains the World Health Organization gold standard front line standard. Experienced cancer physicians have all used doses far above the standard dose for short term, post op or orthopedic pain seen in a non-cancer patient. Cancer pain, especially during hospice care can be chronic and unremitting and as discussed below, we know there is large inter-patient pharmacologic variability either at the opioid receptor or classically studied parameters of drug metabolism.

Govoni and colleagues (2008) provide a recent review of the known polymorphisms in the μ opioid receptor as well as of COMT (catechol-o-methyl transferase). There are already about 100 variants of the μ -receptor gene (OPRM1) and at least one important, functional variation in the COMT gene. It is clear that patients who are compound heterozygotes for these proteins need very different doses of morphine to attain analgesia. More over there are significant polymorphisms in the metabolism of and excretion of morphine based upon polymorphisms in the cytochrome P450 family of enzymes. This system is responsible for many of the drugs we use. CYP2D6 is important in about 25% of drug metabolism.

The ABC family of efflux pumps also has functional polymorphisms altering the kinetics of opioids and anti-neoplastics. The practical importance of knowing about these host (aka patient) characteristics is that as we prescribe pain medicine we are aware of the possibility that dosing can vary by 5-10 fold between patients and there are even some variants that result in the inability to activate/metabolize drugs such as codeine. Even with respect to morphine, the differences in the hepatic metabolism of morphine to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) will affect therapy. M6G has analgesic properties and M3G, the main metabolite has antagonist activity and also be responsible for side effects (discussed in Govoni et al., 2008). A recent

excellent review summarizes the rapidly expanding area of pharmacogenetics (Holmes et al., 2009).

With respect to other opioids, I would offer several brief comments: the synthetic opioids such as buprenorphine and fentanyl also have specific metabolic fates and their potency is dependent upon parent drug for the former and on free drug in the bloodstream for the latter respectively. There are additional narcotics such as oxycodone and μ receptor agonists such as tramadol that are not discussed here. From a practical point of view, I generally start with morphine and escalate the dose as needed. Switching to other agents is because of the rare allergy, side effects and toxicity and/or tolerance or patient preference for any reason. As a matter of practice, I personally do not use meperidine in pediatrics. The dosing is 10 times greater than morphine so I always remain concerned about prescribing an overdose if I start with it and then switch to morphine. Also normeperidine is a partial antagonist with a prolonged half life and can cause seizures. On the other hand despite cultural implications, at least in the United States, methadone, with a prolonged half life compared to morphine has provided much needed, facile oral dosing for some patients and may be under utilized compared to other longer acting agents in this class. The choice of opioid may vary by availability and custom but as long as the used correctly, effective analgesia can usually be attained.

The significance of noting just some of the pharmacokinetic issues here is not so that we routinely measure these compounds as we sometimes do with anti-epileptic medicines or follow kinetics of some anti-cancer drugs but to serve as a reminder that we need to be cognizant of the potential marked variability between patients and drug interactions so that in the real world, we are more comfortable treating patients with the amount of drug required to eliminate suffering without being overly concerned with the absolute dosing.

Conclusions

This very brief discussion of cancer related symptoms should serve to remind us that: A) somatic and psychological issues co-exist; B) that pain is very often associated with and likely exacerbates depression; C) the pain and fatigue of cancer are results of complex interactions of tumor and patient and biochemically caused by inflammatory and immunomodulatory molecules; and D) the treatment of a patient's symptoms may depend upon the polymorphisms for drug receptors, drug metabolism and other polymorphisms in the cytokine family. The ultimate treatment is removal of the cause, but for most patients with advance cancer (estimated to be about 10,000,000 world wide on an annual basis) this is not possible so that we are left with treatment of the symptom(s).

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