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SHORT COMMUNICATION

Total pain, opioids, and immune checkpoint inhibitors in the survival of patients with cancer

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Experimental and observational studies have shown that opioid analgesics may increase tumor growth, potentially reduce immunotherapy efficacy, and shorten survival. As a result of the lack of clinical data, the current rationale for continuing opioid analgesic treatment is based on animal models, which suggests that physical pain itself may potentially influence cancer growth and exert immunosuppressive effects. Total pain encompasses the various factors that patients may experience during their cancer journey: physical symptoms, social isolation/loneliness, psychological, spiritual/existential, and financial distress. These need to be screened and discussed with patients to help them cope with the treatment and disease. As each issue may affect survival, it is essential to identify them to understand how they might affect the patient's immune system, influence immunotherapy outcomes, and ultimately, survival. The question arises whether a single factor, such as the combination of opioids and immune checkpoint inhibitors, negatively affects treatment outcomes. While there is a risk of fostering opioid phobia, the complex interplay between total pain, quality of life, and the immune system must be considered. Thus, in studies that appropriately investigate the interactions between opioid analgesics and the immune system, it is essential to consider all the distress factors that patients may experience at each stage of their illness.

Key words: opioids, total pain, immune checkpoint inhibitors, cancer, survival

Experimental and observational studies have suggested that opioids, via the hypothalamic—pituitary—adrenal axis, may increase tumor growth, increase risk of infection, potentially reduce immunotherapy efficacy,[1] and shorten survival.[1]

However, robust clinical evidence about the immune and endocrine effects of opioids on patients with cancer is absent.[1-4]

Immune checkpoint inhibitors (ICIs) for primary malignancies are prescribed in both adjuvant and neoadjuvant settings and administered until the late stages of life.[5] Given the negative interaction between ICIs, antibiotics, corticosteroids, and paracetamol, prospective studies involving large samples are needed to determine whether the concomitant use of other drugs such as opioids reduces the efficacy of ICIs and shortens survival.[4,6]

As a result of the lack of clinical data, current evidence[1-4] for continuing opioid analgesic treatment is based on animal models,[1] which suggest that physical pain itself may potentially influence cancer growth and exert immunosuppressive effects through the increased release of endogenous opioids. In addition, because the possible negative effects of opioids on survival appear to be dose related, the lowest effective dose of opioids can be recommended,[3] and the dosage gradually increased as needed and combined with non-opioid analgesics (adjuvants and nonsteroid anti-inflammatory drugs) and/or nerve blocks to keep the opioid dose low.[7]

If opioid-related reduced survival were demonstrated in patients treated with immunotherapy, managing their pain would become very difficult at any stage of the disease, and particularly at the end of life, because currently we have no alternatives.

As many patients with cancer experience intense perioperative pain during disease, withholding opioids would be unethical because of exposing these patients to possibly unbearable pain. Moreover, opioids relieve dyspnea and psychological distress, thus improving patients' quality of life.

The indication[1-3] for gradually increasing opioid dosage, so-called opioid titration, is well-known to pain therapists and palliative care specialists.[7] All available options should be considered and used for everyone to minimize the required opioid dose.

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Currently, experimental data do not allow us to estimate the effect size of opioids on tumor growth and survival, so there is no reason to suspend their use if they are necessary for pain relief.

Until data are available on the impact of opioids on tumor growth and survival in patients treated with immunotherapy, there is no reason to suspend opioid therapy.

An approach that includes careful listening to the patient, thorough examination, and patient-reported outcomes[8] on pain intensity, as well as physical and psychological symptoms, is crucial for assessing the type (neuropathic or somatic), intensity, causes, sites, and triggers of pain.[7]

However, is it appropriate to focus only on drugs that may interfere with survival, without also considering the impact of psychosocial and spiritual factors on immunity and survival in patients with cancer?

Without incorporating the concept of 'total pain' as described by Cecily Saunders,[9] physical assessment alone is insufficient. Total pain encompasses various factors that patients may experience during their cancer journey: physical symptoms, social isolation and loneliness, psychological, spiritual/existential, and financial distress. These factors also need to be screened, assessed, and discussed with patients to help them cope with the treatment and the disease. As each problem may impact survival, it is important to identify them to understand how they might affect the patient's immune system and influence immunotherapy and survival.

'Total pain' is a complex syndrome with many dimensions and addressing some components may help alleviate others, including physical pain, thereby potentially reducing opioid requirements.

A clinical examination that does not identify these factors may result in prescribing higher doses of opioid medications without first addressing the total pain. Proper evaluation of total pain might reduce the need for opioids or higher doses.

This is the rationale for asking patients about psychological distress, financial worries related to their illness, spiritual pain, and social isolation. Initial responses should be collected and reviewed for initial screening before proceeding with more detailed investigations using validated instruments as needed.[10]

PSYCHOLOGICAL DISTRESS

Depression, which can occur at any stage of illness, including among long-term cancer survivors,[11] is estimated to affect approximately one in four patients with cancer. These patients are five times more likely to experience depression than the general population.[11] Anxiety and depression have been linked to cancer incidence and survival[11,12] and can interfere with treatment adherence, as well as weaken the immune system's resistance to active disease.

The body's inflammatory response and the tumor microenvironment are linked to psychological distress through the immune system.[12] Chronic psychological distress can reduce the efficacy of anti-programmed death-ligand 1 (PD-L1) immunotherapy,[12] whereas antidepressants such as imipramine and amitriptyline can exert positive effects on the immune system.[12] When used in conjunction with PD-L1 antibodies, these antidepressants can work in synergy to inhibit tumor growth.[12] This underscores the importance of screening for psychological symptoms, assessing them with validated tools, and monitoring them closely.

Antidepressants such as amitriptyline and duloxetine, which are central to treating neuropathic pain, can often reduce the need for higher opioid doses when used in combination treatment.[7] Effective management of anxiety and depressive disorders in cancer settings is primarily achieved through psychotherapeutic and psychopharmacological approaches, often with the assistance of specialists.[11]

FINANCIAL DISTRESS/TOXICITY

Financial distress can arise at diagnosis, during initial and ongoing treatment, at the end of life, and among survivors.[13] It has been linked to clinically relevant outcomes, such as health-related quality of life (HRQoL), symptom burden, treatment compliance, and survival during treatment.[13]

Stress or worry over medical expenses is reported by 22%-64% of patients with cancer and their caregivers.[14] Greater financial distress leads to greater psychological distress, particularly among patients with cancer who are at risk for severe emotional distress, anxiety, and depression.[10] This distress can result in delayed diagnoses and reduced adherence to treatment.[14,15]

Financial toxicity was reported by 26% of 3670 study patients and was strongly correlated with worse global quality of life at baseline. Financial toxicity predicted a greater likelihood of worse HRQoL scores (odds ratio 1.35, 95% confidence interval 1.08-1.70, $P = 0.009$). During treatment, 22.5% of patients reported financial toxicity, which was significantly associated with an increased risk of death (hazard ratio 1.20, 95% confidence interval 1.05-1.37, $P = 0.007$).[16] Conversely, screening and intervention for financial toxicity in patients with hematologic malignancies have been linked to better quality of life and longer survival.[17]

SPIRITUAL PAIN

In their recent systematic review and process-based analysis of quality evidence and expert consensus concerning spirituality in serious illness and health, Balboni et al.[18] identified key implications for patient care and health outcomes. Of the 8946 records retrieved, 371 met the inclusion criteria for serious illness, with 76.9% having low-to-moderate risk of bias. The review concluded that spiritual care should be routinely incorporated into the medical care of patients with serious illnesses. Up to 99% of patients report having spiritual needs, and the provision of spiritual care was associated with improved end-of-life outcomes and QoL. In

addition, frequent attendance at religious services was associated with a lower risk of mortality, and a dose—response association was observed between attendance and reduced mortality risk,[18] as well as the incidence of depression.[18]

SOCIAL ISOLATION AND LONELINESS

Experimental and observational evidence suggests that social isolation and loneliness can exert unique and independent effects on the endocrine and immune systems through the hypothalamic—pituitary—adrenal axis,[19-21] and are associated with an increased risk of early mortality. A cancer diagnosis is a stressful event that heightens distress, and stressors can predict loneliness. Emotional loneliness is a common source of distress and is closely correlated with depression.[19]

Moreover, loneliness is a distressing experience, especially in the period following initial treatment. Social support can extend the survival of patients with cancer. Possible explanations are that instrumental support improves accessibility to healthcare, while emotional support reduces stress and may enhance immune response. Higher mortality rates among patients with cancer have been linked to a lack of close relatives, friends, or living children.[22]

During a 29-month follow-up, and after controlling for diverse factors (e.g. age, sex, chronic disease, alcohol and tobacco use, performance status), Penninx et al.[23] found that loneliness predicted all-cause mortality and that immunity might be suppressed in lonely individuals. In addition, lonely individuals may experience worse outcomes when they are ill than their nonlonely counterparts.[24]

Many factors influence the interaction between the immune system and the survival of patients with cancer. The question arises whether a single factor, such as the combination of opioids and ICIs, negatively affects treatment outcomes. While more evidence is needed, we believe the answer is more complex and involves evaluating total pain. Although there is a risk of fostering opioid phobia, which we aim to address, the complex interplay between total pain, quality of life, and the immune system must be considered.

While the total pain experienced by patients with cancer may not be fully alleviated by opioid use alone, patients benefit from being asked simple questions, being listened to by a multidisciplinary care team, and being adequately managed. Can this impact their experience in a way that alters the immune system more than the use of single drugs? We need evidence to confirm that. Thus, in studies that appropriately investigate the interactions between opioid analgesics and the immune system, it is essential to consider all the distress factors that patients with cancer may experience at each stage of their illness.

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DISCLOSURE

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