Pharmacotherapy for refractory cancer pain

An essay

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Dedication

To my Mother and Father

for encouragement, support , understanding and love.

To My Sister *Dr. May and my* Brother *Hassan*

for supporting, understanding and giving me the help to finish this work

To My Beloved Husband Dr. Ahmed Abdellattif

For being by my side all through

To the soul of Prof Dr Mohamed Omar Tawfik

Who inspired me to do this work

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ABSTRACT

The most effective and most appropriate treatment for moderate to severe cancer-induced pain, and they remain the best front-line treatment for cancer pain patients. However, care must be taken to closely monitor patients for potential adverse effects of opioids.

KEY WORDS

Pharmacotherapy

Refractory

pain

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List of Abbreviations

5-HT	5-hydroxytreptamine (serotonin).
ACE	Angiotensin converting enzyme.
ATC	Around the clock
BTP	Breakthrough pain.
CAMP	Cyclic adenosine monophosphate.
COX-1	Cyclooxygenases 1.
COX-2	Cyclooxygenases 2.
CSI	Continuous subcutaneous infusion.
CVA	Cerebrovascular accident.
CYP 450	Cytrochrome P-450.
DPH	Dextropropoxyphene.
FBT	Fentanyl buccal tablet.
GABA	gamma-aminobutyric acid type B.
IRM	Immediate-release morphine.
MAOI	Monoamine inhibitor.
MG3	Morphine-3-glucuronide.
MG6	Morphine-6-glucuronide.
MI	Myocardial infarction.

MOR	Mu-Opioid receptor.
N/A	Not available.
NMDA	N-methyl-D-aspartate.
NSAIDs	Non steroidal anti-inflammatory drugs.
OEI	Opioid escalation index.
OIN	Opioid induced neurotoxicity**.**
OTFC	Oral-Transmucosal fentanyl citrate.
PCA	Patient controlled analgesia.
PGH2	Prostaglandin H2.
PGI2	Prostaglandin I2.
ROS	Reactive oxygen species.
SSRI	Serotonin-selective-reuptake inhibitor
TCAs	Tricyclic antidepressants
TTS	Through the skin.
TXA2	Thromboxane A2.
VAS	Visual analogue scale.
WHO	World health organization.

INTRODUCTION

Introduction

Pain is the first symptom of cancer in 20–50% of all cancer patients, and 75–90% of advanced or terminal cancer patients suffer from chronic pain syndromes related to chemotherapy, failed treatment, and/or tumor progression.[1, 2]

Cancer patients can experience pain with varying degrees of intensity and frequency at multiple anatomical locations. Cancer pain is multifaceted, with clinical descriptors including acute, chronic, nociceptive (somatic), visceral, and neuropathic[3] It consists of complex mixtures of nociceptive and neuropathic types of pain that are likely to be driven through different mechanisms.[3]

Although opioids are recommended for treatment of moderate to severe cancer pain, several barriers can limit the effective treatment of such pain[3] Many of these barriers hinge on opioid related concerns held by physicians, patients, and patients' families[3] Adding to concerns related to fear of addiction, opioid administration can be associated with severe, sometimes debilitating side effects including somnolence, mental confusion, and constipation.[4]

Moreover, some patients develop analgesic tolerance to opioids, in which greater doses of opioids are required to produce effective pain management.[3, 5]

Importantly, the chronic nature of cancer pain often requires prolonged opioid administration through controlled-release tablets, repeated bolus injections, or transdermal patches.[6-8]

Another potential problem with the use of opioids in treating cancer pain is decreased analgesic efficacy, which can potentially arise from multiple mechanisms, including the development of receptor desensitization,

opioid-induced hyperalgesia, subtle and intermittent withdrawal, and psychological factors.[5, 9]

In addition, increased doses of opioids may be required because of advancement of the disease, resulting in greater pain[10]. Clinical studies have reported that opioids administered by different routes of administration (transdermal, oral, intrathecal, and intravenous) can unexpectedly produce hyperalgesia and allodynia, particularly during rapid dose escalation.[11]

Successful opioid treatment of any duration depends on achieving a favorable balance between analgesia and adverse effects[1, 12] Importantly, there is great interindividual variability in opioid effects; even with a similar type or severity of pain, the effective opioid dose as well as the relative toxicity ratios may vary greatly across patients.[1, 12]

Effective pain management with opioids is dependent on understanding of opioid pharmacology, including different formulations, the impact of route of administration, and the potential for interactions with concurrent medications. These concepts are important for selection of the initial opioid, as well as for opioid switching and rotation, to maintain effective pain management.

Antipyretic analgesics are the first line of implementation according to the sequence-staged scheme of the World Health Organization (WHO) for cancer pain.With progressive incrementation in the pain state; their use is supplemented by the addition of opioid drugs. The efficacy of NSAIDs in patients with tumor pain has been shown in numerous clinical trials.[49, 50]

Coanalgesics are drugs administered in conjunction with NSAIDS and opioids that may enhance the analgesic activity of the NSAIDs or opioids,

have independent analgesic activity in certain pain states, such as neuropathic pain, or may counteract some of the adverse side effects associated with NSAIDS or opioids.[1]

Clinically, Coanalgesics consist of a diverse range of drug classes, including anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors), N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine), corticosteroids, skeletal muscle relaxants, local anesthetics, and alpha-2 adrenergic agonists (e.g., clonidine)[1] Coanalgesics are frequently administered with opioids in efforts to diminish the dose required for effective pain management and reduce adverse effects.[13]

Moreover, the use of coanalgesics that target neuropathic pain may be particularly important because such pain is resistant to opioids, and it occurs in 40–50% of patients with cancer pain.[14]

Overall, multimodal therapy for pain management is recommended[1] for two main reasons: (I) Coadministration of adjuvants that block adverse effects such as nausea, constipation, and opioid-induced hyperalgesia will improve pain management and decrease adverse side effects, thus improving the patient’s quality of life; and (II) Combination pharmacotherapy is often better than opioids alone due to multiple mechanisms of action, particularly given the multifaceted nature of cancer pain regarding neuropathic, inflammatory, and mechanical qualities.[1,15]