Biomarkers and predictors of efficacy of analgesics in the management of cancer pain

Adam Bobrowski, MD(C)[1], Arnav Agarwal, MD(C)[1], Leigha Rowbottom, MD(C)[1], Rachel McDonald, MD(C)[1], Anthony Furfari, MD(C)[1], Stephanie Chan, BSc(C)[1], Pearl Zaki, BSc(C)[1], Bo Angela Wan, MPhil[1], Henry Lam, MLS[1], Azar Azad, PhD[2,3,4], Ronald Chow, BMSc(C)[1], Edward Chow, MBBS[1], George S. Charames, PhD[3,4,5], Carlo DeAngelis, PharmD[1]

[1]Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; [2]Mount Sinai Services Inc., Toronto, Ontario, Canada; [3]Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada; [4]Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada; [5]Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario, Canada

Radiation Oncology UNIVERSITY OF TORONTO

Sunnybrook HEALTH SCIENCES CENTRE

Introduction

- Cancer pain is a significant burden to patients and a major therapeutic challenge for physicians.
- Inter-individual differences in responses to both opioids and non-opioids exist. Genetic variations and SNVs have been attributed to these differences in analgesic efficacy and toxicity, and consequently affect dosing protocols.
- The purpose of this literature review is to present state-of-the-art evidence regarding biomarkers significantly associated with analgesic efficacy and toxicity related to treatment for cancer pain.

Materials and Methods

- A comprehensive literature search was conducted in Ovid MEDLINE and Embase Classic and Embase The following keywords were used: “cancer”, “pain”, “pain management”, “biomarkers”, “genetics”, “genomics”, and “alleles.” Titles and abstracts of all articles were screened for relevancy independently by two authors (AA, AB). If the articles were thought to be relevant based on the eligibility criteria by both authors, full-text publications were retrieved and examined for relevancy.
- Any discrepancies were resolved by discussion amongst the two authors, with adjudication by a third reviewer (AF).

Results

μ-Opioid Receptor (OPRM)

- **Klepstad et al.**: Homozygous for the 118G allele of *OPRM* required greater analgesic doses to achieve pain control. No differences observed in the -172 G>T, the IVS2+31 G>A, and the IVS2+691 G>C variants.
- **Reyes-Gibby et al.**: Carriers of the GG or AG genotypes needed higher morphine dose compared to their patients of the AA genotype to achieve sufficient analgesia (93% more for GG, 18% more for AG).
- In contrast, a Japanese study found no correlation between the *OPRM* variant and the dose of morphine required to achieve analgesia. **Ross et al.** examined 7 *OPRM* SNVs and found no significant differences in genotypic or allelic frequencies between morphine responders and opioid switchers.

Catechol-O-methyltransferase (COMT)

- **Rakvåg et al.**: Carriers of haplotype 1 and of the A allele for the rs4680 variant required lower morphine doses to relieve pain. This variant was associated with a 3 to 4-fold reduction in the activity of the COMT enzyme and an effective increase in dopamine signaling, causing a consequent reduction in levels of encephalin peptides in neurons. This causes an up-regulation of mu-opioid peptides and an alteration in pain sensitivity, where carriers of haplotype 1 required less morphine than non-carriers.
- **Ross et al.**: *COMT* SNVs in intron 1, particularly at position -4873G to be significantly and independently associated with morphine-induced side effects in a population of 228 cancer patients experiencing moderate to severe pain. Pain was cited as the primary motivation for opioid cycling, the induction of adverse events such as confusion, drowsiness, nightmares and hallucinations were important contributing factors.

Multi-Drug Resistance 1 (ABCB1)

- **Oliveira et al.**: Homozygotes of the C3435T T allele have less mRNA, while homozygotes of the C3436T T allele have higher dosing requirements.
- **Ross et al.**: Carriers of SNV G2677T/A in exon 26 were less likely to experience morphine side effects than individuals presenting A or T alleles at this site.

OPRM1, COMT* and *MDR1

- **Oliveira et al.:** Total oral morphine equivalent consumption was only significantly correlated to carriers of the Met allele in rs4680. Individuals of this genotype required higher opioid dosing in order to achieve sufficient analgesia.
- **Reyes-Gibby et al.:** Compared to Met/Met homozygotes, cancer patients with the Val/Val and Val/Met genotypes had higher morphine requirements of 63% and 23%, respectively. Patients of the *OPRM1* AA and *COMT* Met/Met genotype required the lowest amount of morphine for analgesia.

β-Arrestin 1* and *2 (ARRB1 & ARRB2)

- **Ross et al.**: The T8622C variant was more likely to occur in opioid switchers. Variation between switchers and controls seen in alleles 1182G/A, 5864G/A, and 11143G/A6.
- **Matsuoka et al.**: Downregulation of *β*-arrestin1 relates to plasma morphine concentration or the required dose of morphine.

Uridine disphosphate-glucuronosyltransferase (UTG2B7)

- Fladvad et al.: Genetic variability in UGT genes contributes to variability in serum morphine glucuronide to morphine concentrations in Caucasian patients. No effect on morphine metabolic ratios was found for variants in the *UGT2B7* gene. Two haplotypes (1a and 1d) in *UGT1A8* and *UGT1A1* were weak predictors for reduced morphine glucuronide to morphine serum levels.
- **Ross et al.:** No difference in *UGT2B7* genotype or morphine/metabolite ratios between opioid switching patients.

Signal Transducer and Activation of Transcription 6 (STAT6)

- Cancer patients unable to tolerate or gain sufficient analgesia from morphine and were transferred to a different opioid were found to have increased carriage of the variant T allele at -1714 and a significant difference in the allelic frequencies at 9065C/T in intron 6 in STAT6.

Bisphosphonates

- **Engler et al.:** Pamidronate therapy reduced serum levels of C-telopeptide of type I collagen and urinary free deoxypyridinoline. These were significant predictors of reduced pain intensity, while total alkaline phosphatase activity was associated with increased pain intensity.
- **Martinetti et al.:** 60mg of intravenous pamidronate had a statistically significant correlation between analgesia and a decrease in ICTP and osterprotegenin.
- **Joerger et al.**: assessed the bone formation marker procollagen 1 type N-propeptide (PINP) as a biomarker for skeletal morbidity in 70 patients with malignant bone disease being treated with 60mg of intravenous pamidronate. Patients with low baseline PINP averaged a 20% or higher reduction in pain, while higher baseline PINP levels were associated with a shorter duration of pain response. The proportion of patients with ongoing pain following 3 bisphosphonate treatment cycles was 18% in a high baseline PINP concentration population and 45% in a low baseline PINP concentration cohort.

Conclusions

- This literature review highlights the variability in drug responsiveness that is based on changes at the molecular level of drug target receptors, drug metabolizing enzymes, and drug transporting proteins that interact to define an altered homeostatic state.
- It can be argued that the use of SNVs and biochemical signals can inform clinicians to administer the right dose for the right person at the right time. Nonetheless, there are several contradictions in the literature.
- Further inquiry and research is required to develop an evidence-based pain management protocol that considers both biochemical and genetic signatures of a patient.

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