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Role of Pharmacogenomics in Cancer Pain

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Abstract

Cancer pain is a devastating complication among most of the cancer patients. Unfortunately it remains untreated or under treated. Various therapies have been used to cure cancer, these include drugs along with chemotherapy, *bisphosphonates*, or calcitonin, radiation therapy, and radionuclide therapy etc. Invasive surgical and nonsurgical treatments, such as acupuncture, nerve blocks, and neuroablation, have also been used for the treatment of cancer-related pain. Each treatment is associated with inter individual variation which may be due to environmental or genetic factors.

Recent advances like completion of human genome and Hap Map projects have created new high throughput techniques of genotyping which are used to correlate various genetic variants and effect of different drugs used for pain relief in cancer patients. Genetic polymorphisms in ABCB1 result in enhanced efficacy, but also adverse effects to many drugs used widely in palliative care. For opioids, a mu receptor polymorphism leads to reduced efficacy for non-steroidal anti-inflammatory drugs; CYP2C9 polymorphisms are associated with a higher risk of bleeding. Different genetic mechanisms act at different levels influencing the important pathways involved in the pharmacokinetics and pharmacodynamics of different drugs. However, this field is still unexplored except opinoid receptors. The main drawback of different studies is lack of consistency of results. In the present review an attempt has been made to summarize the pharmacogenetic knowledge to manage pain among cancer patients.

Keywords: Cancer; Pharmacogenomics; Opioids; Cytochrome P450; μ-opioid receptor gene (OPRM1); Tremadol; Oxicodone; Hydrocodone

Introduction

Cancer is a shattering disease that is most of the associated with pain, and depression. The treatment of pain include opioids, and number of adjuvant analgesics. Most of the pain relief measures used are poor predictors. Further research is needed to evaluate its clinical importance in cancer pain management. There are no standard norms/dosages of different drugs to be used to relieve cancer patients from pain this may be due to the fact that different individuals behave differently for standard dosage of drug for many cancers. Different analgesics are being used to manage pain. Some of the drugs do not cause pain relief, many drugs some time may lead to life-threatening adverse drug reactions that may be due to drug-drug interaction, the rate of drug absorption, distribution, metabolism, elimination and important molecular pathways that involves series of interactions of different drug molecules in a cell. Inter individual variation of drug dosage has lead to the informtion about pharmacogenomics (PGx), this deals with the study showing how genes impact the response to a drug. This branch of science has brought a shift towards personalized medicine. Till date many drugs have been used in a uniform manner without taking into consideration the genetic makeup of the individual patients. PGx testing now allows for a more individualized approach for both pharmaceutical and therapeutic mediations. New drug molecules have come into light to cure cancer related pain. The inter individual variation may be due to differences in the single nucleotides (SNPs) present in the DNA sequences. Some of the SNPs encode metabolizing enzymes, or drug transporters therefore affecting the drug action [1]. The reason of different responses to a drug may be due to sequence differences in different genes which encode different proteins which may be responsible for controlling the metabolism of drugs. Interestingly different individuals respond differently to different drugs the responses may be categorized into low responses or moderate or severe side-effects. With the recent development and mapping of human genome project it is now known that these differences may be due to of one or more gene variants. It is important to notice that all gene variants may not result into the reduced drug effect. Different patients may have multiple copies of the “normal” or wild type gene for a drug metabolizing enzymes. Reduced drug metabolism may be due to the mutations in the normal SNP responsible for enzyme inactivation.

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That results in the higher plasma concentrations and lower clearance rates and finally into adverse drug reactions.

Among cancer patients the effective analgesics used are opioids that decrease the pain. The threshold of pain varies from individual to individual which may be associated with the genetic variability among different populations. It is estimated to be present in 20-50% of the patients [2]. Pain have been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage [3]. Approximately 80% of patients with advanced-stage of cancer show moderate to severe pain [4]. A meta-analysis conducted revealed that approximately 50% of the patients suffer from pain [5]. Younger patients show more pain as compared to the older patients [6]. There are multiple sites of pain [7]. Pain have been scored into the category of 4 to 6 while very high pain is scored as seven. MUHC (McGill University Health Center Cancer Pain Clinic) opted for a personalized approach that includes pharmacological and non-pharmacological therapies. The center carried out two visits and labeled these visits into baseline and follow-ups and named them as FU1, FU 2. This study included patients with symptom severity measured by the Edmonton Symptom Assessment scale, and pain and disability measured with the Brief Pain Inventory, and analgesic plan implementation [8]. They observed that pain management require many approaches for the pain relief in both the groups.

Different Mechanisms of Cancer Pain

Cancer pain is mostly very severe and uncontrollable. It depends upon many factors like nature of cancer, and the site where the metastases has occurred, hence different patients behave differently e.g. metastatic breast cancer to the spine will develop clinical signs different from the patient who acquires oral cancer. Fortunately few cancers do not develop pain for instance patient with squamous cell carcinoma of the lung is very rarely associated with pain, however, if it occurs in the oral cavity it is linked to pain as an initial symptom. Pain have been scored on the basis of pain severity into three categories i.e. mild-moderate and severe. This range further suggests different treatment modalities. Different drugs are used to manage the pain. Commonly used are opioids. These are used as analgesics for the management of cancer pain. The cancer pain depends on the histology which defines the type of the cancer; the location of the primary neoplasm is estimated the location of metastases is also defined.

Various animal models have provided mechanisms involved in the cancer pain. It has been proposed that endothelin-1 (ET-1) plays an important role in cancer pain. ET-1 impasses to two G protein–coupled receptors, the endothelin-A receptor (ET_AR) and the endothelin-B receptor (ET_BR). ET_ARs are disseminated on peripheral sensory neurons; ET_BRs are expressed on non myelinating Schwann cells of the sciatic nerve and dorsal root ganglion satellite cells as well as on keratinocytes. The ET_AR primarily mediates vaso and bronchoconstriction, mitogenesis, anti-apoptosis, and acute pain. ET_AR antagonists prevent osteoblast proliferation and bone metastases proliferation these receptors facilitates in flammatory pain and vasodilatation. Different animal models have been used to study different receptors and pain severity in cancer. Increased ET-1 levels in whole tumor manifest hyperalgesia. A local nociceptive effect was observed when ET-1 was injected directly into the tumor in a experimental model. ET-1 injection and antagonism contributes to tumor-induced nociception. It has been shown that vasoactive peptide Bradykinin (BK) is involved in the cancer pain. Certain cancers, such as prostate, secrete kallikrein, result into increase in the concentration of Bradykinin (BK) in the cancer micro environment. Bradykinin directly regulates endothelin-1. Nerve growth factors are also involved in the cancer pain. Chronic NGF exposure leads to an increase in the expression of TRPV1 receptors in sensory neurons and increases ASIC expression and bradykin in receptor contributing to pain this may be due to "perineural involvement which involves invasion and proliferation of cancer within a nerve, associated with pain and recurrence following surgical resection. Other factors are immunological mediators like cytokines and tumor necrosis factor which promote pain in cancer

Use of Analgesics and Cancer Pain

Opioids

Opioids are safe and can be controlled by multiple routes, the dosage can be easily titrated, these are highly effective for all kinds of pains i.e. somatic, visceral, neuropathic etc. Most difficult pain to be treated is neuropathic pain opioid-based analgesia is effectively used. The G-protein coupled receptors are present in the brain and spinal cord which interact with the opinoid receptors causing opinoids to start their function. Opinoid receptors are mu, kappa and delta All these receptors behave differently. Delta receptors are the natural target for enkephalins. The mu-opioid receptor is the primary site of action of opioid analgesics including morphine, fentanyl, and methadone. Currently prescribed opioids are mu-opioid receptor agonists. The kappa and delta-opioid receptors have been cloned. As described above most of the prescribed opioids are mu-opioid receptor agonists, they exhibit overlapping affinity with kappa receptors. Currently many genes have been studied to identify pharmacogenomic markers for opioid therapy. There are approximately 100 polymorphism involved in the mu-opioids receptors, the genes implicated in the pharmacodynamics are OPRM1, COMT and in the pharmacokinetics areCYP2D6, CYP3A4/5, ABCB1 of opioids [9]. cDNA encoding an "orphan" receptors have been identified showing high degree of homology to the "classical" opioid receptors at the structural level this receptor is an opioid receptor and is designated as ORL1.

Opioids transporters and their pharmacokinetics

Disposition of many drugs including opioids [10] require drug transporters these can modulate the pharmacokinetics, pharmacodynamics and their associated drug-drug interactions (DDIs).

Adenosine triphosphate-binding cassette (ABC) transporters like P-glycoprotein (P-gp; ABCB1, MDR1), BCRP (ABCG2) and MRPs (ABCCs) are present at the blood-brain barrier (BBB), gastrointestinal tract, liver and kidneys [10]. These are important transporters as they show impact on the absorption, distribution, and elimination of many drugs, including opioids. [11]. The PK-PD relationship can be evaluated using opioid drugs [12]. The effects of morphine, methadone, and loperamide are modulated by P-gp [12]. Opioid drugs and some of their active metabolites interact with ABC transporters and reveal new mechanisms that may be responsible for the variability of the response. Opioids exposure may alter the expression of ABC transporters. P-gp can be produced extensively [13] during morphine treatment, revealing the direct or, indirect action. Exposure to opioids may result into the variations in cerebral neurotransmitters causing release of cytokines during pain that may act as a stimulus affecting transporter synthesis.

Adenosine triphosphate-binding cassette has a very intricate

genetic makeup. Numerous SNPs have been reported in the ABCB1 gene which is located on 7q21.12. ABC genes have been divided into seven subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20). The protein product of this gene is a member of the MDR/TAP subfamily. Members of the MDR/TAP subfamily are involved in the multi -drug resistance. This gene is highly expressed in cancer cells [14]. The protein determined by this gene is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity. It is accountable for a smaller amount of drug buildup in multidrug-resistant cells and often enables the progress of resistance to anticancer drugs. This protein also act as a transporter in the blood-brain barrier with substantial LD (linkage disequilibrium) [15,16] ABCB1 gene carries >50 SNPs. Common SNPs encoding this gene are synonymous 1236C>T and 3435C>T and non -synonymous 2677G>T (Ala899 Ser). The incidence of this gene varies in different populations. The frequency of G variant allele is less (10-15%) among Caucasians as compared to Asians (50%). It has been noticed that if healthy individuals are induced pain experimentally by electrical stimulation and further treated with alfentanil there is 3 fold decrease in pain if the individual carries two copies of G allele and 10 fold decrease in respiratory depressant effect [17]. Among cancer patient it has been noticed that there is lot of inter individual variability among patient with single copy of G allele or homozygous for G allele. The non-synonymous SNP, C3435T, occurs with a frequency of 50 – 60% in Caucasians, 40 – 50% of Asians, and 10 – 30% in Africans. It is in strong LD with other SNPs in the ABCB1 gene hence create a haplotype constituting of 3435C>T combined with G>T. A significant relationship between 3435 genotype and the extent of loperamide miotic effects following P-gp inhibition by quinidine have been reported. It has been shown that the brain distribution of morphine, which is transported by P-gp with less efficiency than loperamide, may be affected by 3435 genotype [10]. The 3435T variant is associated with down regulation of mRNA expression, resulting in the low protein expression, in some tissues [11]. These results vary.

Difference in pain relief and opioid doses differ between wild and mutant genotypes. Pharmacokinetic modeling have been undertaken for morphine in plasma and cerebrospinal fluid showing a significant association between the homozygous mutant genotype and increased morphine cerebrospinal fluid concentrations. Further the importance of ABCB1 haplotypes, over the individual SNPs have been demonstrated, some of these haplotypes predict P-gp expression and function [13]. Investigation of haplotypes of 2677 and 3435 SNPs show that subjects carrying the ABCB1 haplotype G2677/T3435 show higher plasma loperamide concentrations than those who do not carry this haplotype [11,14,15,16].

Cytochrome P450

Cytochrome P450 enzymes are vital for the metabolism of many drugs and contain approximately 50 enzymes out of these six enzymes metabolize 90 percent of drugs, two most significant enzymes are CYP3A4 and CYP2D6. These enzymes show the high degree of inconsistency. Genetic variability that may impact the patient's response. Most frequently given drugs are beta blockers and antidepressants. Cytochrome P450 enzymes result into inhibition or induction by some of these drugs, causing significant drug-drug interactions hence therapeutic failures. Genetic testing can postulate if a patient has beneficial or harmful enzyme polymorphism. There are 57 putatively functional genes and 58 pseudo genes that are grouped into 44 subfamilies and 14 families. All these genes are distributed on autosomal chromosomes and are involved in the biosynthesis of steroid hormones, prostaglandins, bile acids, and other. Approximately 12 enzymes belong to 1, 2, and 3 CYP-families. These enzymes contribute in the metabolism of numerous drugs and other xenobiotics. CYP3A4 enzyme covers many protein inhibitors which may or may not be involved in the opioids metabolism. Some of the opioids involved in the metabolism are methadone, oxycodone, hydrocodone, fentanyl, unfortunately, no data is available to reveal the genetic association of these enzymes with the opioid response. CYP2D6 a cytochrome P450 enzyme covers metabolism of approximately 25% of all drug therapies, including codeine, hydrocodone, oxycodone, and tramadol, as well as tricyclic antidepressants depending upon the phenotype. These therapies are grouped into 4 major groups such as poor metabolizers (5%–10%), intermediate metabolizers (2%–11%), extensive metabolizers (77%–92%), and ultra-rapid metabolizers (1%–2%) (21) This data is available from the European populations and require further validation in other populations of different ethenicities. Patients carrying different genotypes may not show effectiveness against pain when treated with codeine, hydrocodone, oxycodone, tramadol, fentanyl and methadone. There exist a significant impact of CYP2D6 genetic variants on drug efficacy and also the adverse-effect. When a patient with cancer and CYP2D6 metabolizer status exists and is treated with CYP3A4 inhibitors most of the time extra dose of codeine is required, such as clarithromycin and voriconazole. Kotlinska-Lemieszek et.al carried out a meta-analysis to find out the clinically significant drug-drug interactions involving opioid analgesics used for pain treatment in patients with cancer. They collected 901 papers and 17 were included in the final analysis and concluded that most common mechanism eliciting drug-drug interactions was an alteration of opioid metabolism by inhibiting the activity of cytochrome P450 3A4 and pharmacodynamic interactions due to the combined effect on opioid, dopaminergic, cholinergic, and serotonergic activity in the central nervous system. It has beed suggested that physicians prescribing opioids should recognize the risk of drug-drug interactions and if possible avoid the use of many drugs [18]. Genetic variation in the cytochrome P450 (CYP) family reveals an important influence on the destiny of pharmaceutical drugs. CYP2D6, CYP2C19 and CYP2C9 gene polymorphisms of P450 (CYP) family and gene duplications of this gene result into the most common differences in phase I metabolism of drugs. Approximately 80% of drugs in use are metabolized by these enzymes. Nearly 5% of Europeans and 1% of Asians do not have CYP2D6 activity, hence are the metabolizers. CYP2C9 is another important drug-metabolizing enzyme that establishes genetic variants. CYP2C9 polymorphism have revealed the importance of the CYP2C9*2 and CYP2C9*3 alleles. High degree of variation is seen in the Phase II drug metabolizing enzymes [18]. Various SNPs are implicated and show variability of CYP2D6 enzyme that show multi-functions controlled by additional polymorphisms in regulatory trans-genes and non -genetic host factors including sex, age, disease, hormonal and diurnal influences etc. CYPs families of 1 to 3 are of major importance for the biotransformation of drugs. Genetic variation in drug metabolizing enzyme genes reveals genetic influence on drug biotransformation [19]. Interestingly, loss-of-function of polymorphisms in CYP genes unexpectedly affects the expression through splicing, rather than transcription [20]. Copy number variants (CNV) may result into the gain-of-function variants resulting into the higher number of functional gene copies in CYP2D6 and CYP2A6 [21] as well as promoter variants (e.g. in CYP2B6, CYP2C19) and amino acid variants with augmented substrate turnover (e.g. in CYP2B6, CYP2C8). Some epigenetic mechanisms

also play their role. As CYP1A and CYP1B enzymes show important metabolism of pro-carcinogens and cellular signaling molecules, their polymorphisms have been widely studied as predisposing factors for various cancers. Genetic variation is classified into poor metabolizers with a frequency of 5-10%, intermediate metabolizers with a frequency of 2-11% wider metabolizers with an incidence of 77-92% high rate metabolizers which occur with comparatively less frequency i.e. only 1% to 2 % [22]. It has been recently reported that notable drug-drug interaction is seen between etizolam and itraconazole which act as poor metabolizers of cytochrome P450 [23].

Tamoxifen (TAM) is often used among breast cancer patients. TAM is metabolized more actively 4-hydroxytamoxifen (4-OH-TAM) and endoxifen by cytochrome P450 (CYP) mainly CYP2D6 and CYP3A4 enzymes. Due to the genetic polymorphisms in CYP2D6 genes, high variation in the clinical outcomes of TAM treatment is observed among women of different populations. New tamoxifen analogs have been established which may show better clinical outcome for poor 2D6 metabolizers [24]. All the percentages shown are not consistent and differ in different ethnicities more so genetic variant show differential effects [25,26,27,28]. The "double hit" of hyperactivation to morphine via CYP2D6 and the reduced inactivation due to blocked CYP3A4 leads to life-threatening respiratory depression [29].

μ-opioid receptor gene (OPRM1)

On chromosome 6q24-q25 the human OPRM1 gene is located its size is around 200Kb. It contains nine exons and 19 splice variants. The gene is controlled by large number of promoters; many SNPs are situated within this gene [30]. One of the SNP known as 118A.G (SNP database [dbSNP] Accession No rs1799971) has been widely studied from the pharmacogenetic angel specially for opioid drugs. It is located in the exon 1 of the gene and the substitution of an adenine (A) with a guanine (G) and results into the amino acid exchange at position 40 of the opioid receptor protein from asparagine to aspartic acid (N40D), causing the loss of an N-glycosylation site in the extracellular region of the receptor [31]. Its frequency is 27%–48% among Asians, 11%–17% among Caucasians, 2.2% in African Americans, and 0.8% in sub-Saharan Africans [32]. A meta-analysis conducted have demonstrated its controversial role in opioid research [33]. It has three forms resulting into three genotypes which could be homozygous G/G, homozygous A/A, and heterozygous G/A. Different studies have measured the effect of polymorphism on the expression of OPRM1 the levels of μ-opioid receptor have been studied by using *in vitro*, *ex vivo*, and *in silico* methods and it has been proposed that some other gene may be oligogenic in nature i.e. other genes reveal their influence on this SNP which may affect the expression profile [34].

Substitution of the A with a G at position 118 of the OPRM1 gene abolishes three transcription factor binding sites while creating a novel exon splice enhancer as well as p53 and a zinc finger protein binding sites, thus revealing a possible direct effect of 118A.G on gene expression and on the processing of heterogeneous nuclear RNA into mature mRNA [35]. As explained earlier we know pain is a multifactorial in nature hence there exist genetic-epigenetic interaction on the effects of the 118A.G SNP and on the level of OPRM1 mRNA [36,37]. In fact, the substitution of an A with a G at gene position +118 introduces a new –C–phosphate–G– (CpG)-methylation site at position +117, leading to an enhanced methylation of OPRM1 (at this site and downstream) and, causes decrease in the gene expression. Differential mRNA levels and receptor protein may be affected due to the presence of 118G on mRNA turn over; but this still needs to be confirmed. After transcription into CHO cells of a complementary (c) DNA representing only the coding region of the OPRM1 and inhibition of transcription with actinomycin D, the mRNA turnover was the same for 118A and 118G variants it has been predicted a secondary structure of mRNA with different sequences at 118G variant show altered folding compared with other permutations that could affect mRNA stability. Finally, it has been hypothesized that the 118G variant may affect OPRM1 gene expression in addition to mRNA translation or post-translational processing or turnover of the μ-opioid receptor protein [38]. The G variant allele has a frequency of 10-15% in Caucasians but almost 50% in Asians and results in reduced opioid effects. A recent paper described the role of the 118A.G SNP in posttranslational mechanisms [39].

The N-glycosylation may affect the expression on the receptors which may be due to the involvement of the correct folding of receptors in the endoplasmic reticulum and, hence, their organization in the plasma membrane. It has been shown that in CHO cells express the human μ-opioid receptor, the variant receptor show low relative molecular mass as compared to the wild-type, resulting into the differential glycosylation status when both the receptors are compared. Pulse-chain experiments on these cells revealed that the two expressed receptors have dissimilar protein stability since the half-life of the mature form of the variant receptor is almost 12 hours that was shorter than the wild-type receptor (almost 28 hours) causing decreased binding ability with both exogenous and endogenous opioids, making augmented human pain resistance. The mechanism of endogenous opioid in body homeostasis is to maintain the regulatory function. The MOR (A118G) gene polymorphism is found to be highly associated with breast cancer risk in a Northeastern Polish population. [40,41].

One of the most important polymorphisms is thiopurine S-methyl transferases (TPMT) that catalyzes the S-methylation of thiopurine drugs. The most extensively studied drug transporter is P-glycoprotein (P-gp/MDR1), however there are not many studies Polymorphisms in drug transporters may change drugs distribution, excretion, and response. Recent advances in molecular research have revealed many of the genes that encode drug targets. Polymorphism in these genes in many cases, have altered the target sensitivity to the specific drug molecule and thus have a intense effect on drug efficacy and toxicity. For example, the β2-adrenoreceptor, which is encoded by the ADRB2 gene, revealed clinical significance of genetic variation in drug targets. The importance of of pharmacogenetics lies in its potential to identify the right drug at the right dose for the right individual. Drugs with a narrow therapeutic index are thought to benefit more from pharmacogenetic studies. For example, warfarin serves as a good practical example of how pharmacogenetics can be utilized prior to the commencement of therapy in order to achieve maximum efficacy and minimum toxicity. As such, pharmacogenetics has the potential to achieve optimal quality use of medicines and to improve the efficacy and safety of both prospective and licensed drugs.

Catechol-O-methyltransferase (COMT) enzyme in pharmacogenomics and cancer pain

Catechol-O-methyltransferase (COMT) inactivates dopamine, epinephrine and norepinephrine in the nervous system. A common functional polymorphism (Val158Met) leads to a three- fourfold

variation in the COMT enzyme activity, the Met form display lower enzymatic activity. The Val158Met polymorphism affects pain perception, and subjects with the Met/Met genotype

Abnormality in the catechol-O-methyltransferase enzyme, inactivates dopamine, epinephrine and norepinephrine in the nervous system that can suppress the function of endogenous opioids (eg, kephalin), increasing the expression of the opioid receptor [42]. Catechol-O-methyltransferase (COMT) is an enzyme that deactivates biologically-active catechols, including neurotransmitters dopamine, noradrenaline, and adrenaline. Above mentioned mechanism is helpful in many physiological processes, including modulation of pain. Genetic variants in the COMT gene show invariable response to common pain conditions, including cancer pain. [43]. The COMT gene show a large number of single nucleotide polymorphisms (SNPs). A common functional polymorphism (Val158Met) leads to a three to four-fold variation in the COMT enzyme activity, the Met form display lower enzymatic activity [44].

Presence of this variant may lead to 3 to 4 fold abridged activity of the COMT enzyme hence increased sensitivity to painful stimuli, it has been shown that Val/Val genotype require the low dosage of morphine for pain relief [45-49]. The Met/Met genotype of COMAT gene is located in the exon 1 of the gene and consists of the substitution of an adenine (A) with guanine (G) resulting into the amino acid exchange at position 40 of the μ-opioid receptor protein from asparagine to aspartic acid (N40D), hence loss of a N-glycosylation site in the extracellular region of the receptor [50]. This allele is present in 27%–48% in Asians, 11%–17% among Caucasians, and lowest in African Americans and sub-Saharan Africans that is only in 2.2%, and 0.8%. This SNP is of clinical importance for opioid therapy. Genotyping of this SNP shows that it has 1 of the 3 genotypes which are homozygous G/G, homozygous A/A, or heterozygous G/A. Interestingly OPRM1 118A.G SNP affects individual sensitivity to pain, opioid efficacy, and opioid-related side effects and tolerance etc. The explained mechanism is that, carriers of the 118G allele needs higher μ-opioid drug doses in order to get pain-relieving effects, and once this effect is attained, the opioid-related side effects may be seen. The 118A.G SNP has biological significance at the molecular level. Patients carrying the 118G allele may show either an unaltered or a higher sensitivity to pain compared with patients homozygous for the 118A allele, depending upon the individual endogenous opioid quality. However, the results are debatable revealed through a meta-analysis [51]. The biochemical and molecular *in vitro* assays have proven that the variant receptor shows higher binding affinity for β-endorphins, that has altered signal transduction cascade, and it has a low expression compared with wild-type OPRM1. Studies using animal models for 118A.G have shown a double effect of the variant receptor, with an apparent gain of function with respect to the response to endogenous opioids but a loss of function with exogenous administration of the opioid drugs. Although patients with this variant have shown a lower pain threshold and a higher drug consumption in order to achieve the drug effect, clinical experiences have demonstrated that patients carrying the variant allele are not affected by the increased opioid consumption in terms of side effects.

Pharmacogenomics of morphine

Among cancer patients, pain is the major problem. Management of pain is a major issue. Morphine is the drug of choice used for analgesic therapy [40]. The genetic factors are SNP variation . in OPRM1, mu opioid receptors are encoded by this gene and the most important target for morphine, these may be under the genetic impact on the effectiveness of opioids. Morphine binds strongly to the μ-opioid receptors having the activity for κ- and δ-opioid receptors. Morphine, when administered orally, results in oral bio availability to the extent of 38%. The major morphine metabolites are from glucuronidation by the hepatic isoenzyme UGT2B7 to inactive morphine-3-glucuronide (approximately 60%) and active morphine-6-glucuronide (up to 10%). CYP2D6 plays a minor role in morphine metabolism. Morphine reveals certain side effects like sedation, nausea, a feeling of warmth, urinary retention, euphoria, reduced ability to concentrate etc. The gravest side effect of morphine is possibly fatal respiratory depression [51].

Hajj et al. [11] have explained how different doses of morphine are required if a particular genetic marker is present in a population. They have also taken the age as a dependent variable as it has been advocated in the earlier studies that patients with advanced age require significantly less morphine than younger patients. As the age advances there is alteration in distribution, metabolism and elimination of drug dealing with the pharmacokinetics of morphine [52,53].

The allele 118G for OPRM1 require the higher dose of morphine than AA patients. It has been reported that AA patients for OPRM1 SNP has significantly lower cognitive function than AG The the role of COMT variant Val158Met polymorphism and morphine requirements. Val/Val genotype need the highest dose of morphin [54]. The synergistic effect was investigated in COMT Val158Met and OPRM1 A118G variants on the efficacy of morphine for cancer pain it was seen that much less dose of morphine is required if both the genotypes are combined [55]. The most benefit will likely be derived by combining these markers to identify patients with a poor-response profile for which an alternative therapy may be preferred.

Wiffen et al have published a review related to oral morphine in cancer pain. They have selected 4241 participants taking into consideration 62 studies. They concluded that oral morphine is good and the review suggested more randomized studies should be carried out [56]. Cancer-related pain and genetic variation of OPRM1, COMT, and ABCB1 were found to be associated with response to morphine, the effect of CYP2D6 variations are well characterized with codeine and tramadol. The evidence is limited for associating the genetic variation and pain response of oxycodone, hydrocodone, and fentanyl in patients with cancer [57].

Codeine is a weak opioid (derived from opium) it affects central nervous system. It is used widely in combination with acetaminophen and aspirin for the management of mild to moderate pain. It is activated to morphine through CYP2D6 [58]. This is a polymorphic gene having three phenotypes poor metabolizer phenotype, extensive metabolizer phenotype, and ultra rapid metabolizer phenotype. Ultra rapid metabolizers show duplication of the gene, due to which the Causing increased enzymatic activity, mutation in the CYP2D6 decreases the activity the homozygous state resulting in poor metabolism [59]. Poor metabolizers show that codeine is less effective [60]. It is estimated that 7–10% of the population does not express functional CYP2D6. Data from a relevant randomized, placebo-controlled, double-blind clinical trial have shown the effect of CYP2D6 polymorphisms on codeine analgesia using an experimental pain model indicated that codeine administration results in analgesia in extensive metabolizers but had no effect in poor metabolizer patients. Furthermore, although poor metabolizers did not receive any analgesic benefit, they had

the same frequency of side effects with extensive metabolizers. In a small study of 11 patients treated with codeine for analgesia after hysterectomy, two patients had no analgesic effect from the codeine, one of whom was subsequently shown to be a CYP2D6 acts as a good metabolizer and converts codeine into an active metabolite, morphine, which provides its analgesic effect. In case CYP2D6 have two inactive copies the codeine will not be effective. On the contrary, if extra copies of CYP2D6 are present these will convert codeine to morphine to a greater extent, however, as a consequence adverse events like sedation and even respiratory depression, confusion, and shallow breathing may be caused [61].

CYP2D6*1 is the wild-type allele result into normal enzyme activity. The CYP2D6 alleles *2, *33, and *35 are also considered to have near-normal activity. About > 80% of individuals have at least one copy of a normal allele (*1 or *2), or two partially functioning alleles they are "normal metabolizers" and have a phenotypically normal response to codeine. Normal metabolizers show a lot of variability, even among individuals with the same haplotype, the reason is not known [61, 62]. However, evidence is lacking on whether genetic testing for these variants will aid optimum codeine dosing or not [63-66].

Tramadol

In most of the patients with cancer and pain is treated with opioid analgesics only, however, combination with adjuvant analgesics can also be referred as co analgesics. Moderate pain can be treated with weak opioids. There exist an varied opinion about the use of opioid analgesics such as tramadol, codeine, dihydrocodeine, and dextropropoxyphene but many a times these opinoids are used for the treatment of moderate cancer pain. One of the most interesting and useful weak opioids is tramadol (Adolonta, Contramal, Nobligan, Top-Algic, Tramal, Tramal Long, Tramal Retard, Tramundin, Trodon, Ultram, Zydol). Many experimental and clinical studies have been performed with tramadol [67] looking at its unique mechanism, analgesic efficacy and adverse reactions.

Tramadol is largely metabolized by the cytochrome P-450 enzyme system in the liver and is excreted by the kidneys. Tramadol undergoes biotransformation in the liver, initially by the phase I reactions (mainly O- and N-demethylation) and later by the phase II reaction.

CYP2D6 is a poor metabolizers and show reduced analgesic response against tramadol as compared to good metabolizers [68-73]. In one of the studies Stamer et al. [73] investigated the impact of the CYP2D6 genotype and CYP2D6 inhibitors on plasma levels of tramadol and M1. They have selected 174 patients, 170 patients who received tramadol 3mg/kg intravenously for postoperative analgesia. Blood samples were taken after 30, 90 and 180 min. Concentrations of M1 differed between the different genotypes (PM, IM (intermediate metabolizers), EM and UM (ultra-rapid metabolizers). Medications preventing CYP2D6 were managed with tramadol. In the PM group, non-response rates to tramadol treatment augmented fourfold compared to the other genotypes. Tramadol may be used for patients who reveal adverse effects like sedation, fatigue and constipation etc. against strong opioids. Mostly this group constituted of older patients and patients with GI tumors; tramadol may be used as an alternative analgesic.

Oxycodone

The oxycodone is metabolized into noroxycodone by CYP3A4. In few individuals approximately 11% CYPD6 converts active metabolite oxymorphone, which show 40-fold higher affinity and 8-fold higher potency for μ-opioid receptors than oxycodone. However, there are only few studies dealing with CYP3A4 variation to oxycodone response , there is data available in healthy volunteers and postoperative patients which show varied results on CYP2D6 polymorphisms and response to oxycodone. In a cross-sectional study of 450 study patients with cancer treated with oxycodone, [74] revealed no difference in the pain intensity. A very recent study on randomized controlled trials where 1258 participants were selected in this group only six studies further included in another group were pooled 23 studies were selected where the number of participant were 2648 out of this 2144 were analyzed for efficacy and 2363 for safety. The study investigated number of different drug comparisons. Collective analysis of three of the four studies equating controlled-release (CR) oxycodone to immediate-release (IR) oxycodone revealed that the ability of CR and IR oxycodone to provide pain relief were similar (standardized mean difference (SMD) 0.1, 95% confidence interval (CI) -0.06 to 0.26; low quality evidence). Pooled analyses of adverse events showed no significant differences between CR and IR oxycodone for asthenia (risk ratio (RR) 0.58, 95% CI 0.2 to 1.68), confusion (RR 0.78, 95% CI 0.2 to 3.02), constipation (RR 0.71, 95% CI 0.45 to 1.13), dizziness/lightheadedness (RR 0.74, 95% CI 0.4 to 1.37), drowsiness/somnolence (RR 1.03, 95% CI 0.69 to 1.54), dry mouth (RR 1.14, 95% CI 0.48 to 2.75), insomnia (RR 1.04, 95% CI 0.31 to 3.53), nausea (RR 0.85, 95% CI 0.56 to 1.28), nervousness (RR 0.57, 95% CI 0.2 to 1.64), pruritus (RR 1.46, 95% CI 0.65 to 3.25), vomiting (RR 0.66, 95% CI 0.38 to 1.15), and discontinuation due to adverse events (RR 0.6, 95% CI 0.29 to 1.22). Three of the four studies found similar results for treatment acceptability. Pooled analysis of seven of the nine studies comparing CR oxycodone to CR morphine indicated that pain relief was significantly better after treatment with CR morphine than CR oxycodone (SMD 0.14, 95% CI 0.01 to 0.27; low quality evidence). However, sensitivity analysis did not corroborate this result (SMD 0.12, 95% CI -0.02 to 0.26). Pooled analyses of adverse events showed no significant differences between CR oxycodone and CR morphine for confusion (RR 1.01 95% CI 0.78 to 1.31), constipation (RR 0.98, 95% CI 0.82 to 1.16), dizziness/lightheadedness (RR 0.76, 95% CI 0.33 to 1.76), drowsiness/somnolence (RR 0.9, 95% CI 0.75 to 1.08), dry mouth (RR 1.01, 95% CI 0.8 to 1.26), dysuria (RR 0.71, 95% CI 0.4 to 1.26), nausea (RR 1.02, 95% CI 0.82 to 1.26), pruritus (RR 0.81, 95% CI 0.51 to 1.29), vomiting (RR 0.94, 95% CI 0.68 to 1.29), and discontinuation due to adverse events (RR 1.06, 95% CI 0.43 to 2.6). However, the RR for hallucinations was significantly lower after treatment with CR oxycodone compared to CR morphine (RR 0.52, 95% CI 0.28 to 0.97). The quality of the evidence was very low for all these adverse events. There were no marked differences in treatment acceptability or quality of life ratings. The remaining studies either compared oxycodone in various formulations or compared oxycodone to different alternative opioids. None of these studies revealed any clear superiority or inferiority of oxycodone for cancer pain, neither as an analgesic agent nor in terms of adverse event rates and treatment acceptability. The quality of this evidence base was limited by the high or unclear risk of bias of the studies and by imprecision due to low or very low event rates or participant numbers for many outcomes [75].

Hydrocodone

CYP2D6 helps in the metabolism of Hydrocodone by the active metabolite hydromorphone with a 10- 33-fold superior affinity for

μ-opioid receptors than hydrocodone [76]. Extra metabolism may take place by the formation of non hydrocodone by both CYP3A4, and non-CYP pathways. Drugs like codeine or hydrocodone have been replaced by more potent opioids. However, there are not many studies available on the pharmacogenomics of hydrocodone specifically among cancer patients. Most of the current literature assessing the effect of CYP3A4/5 on pain outcomes includes the postoperative patient population, however, no significant association have been established [77]. Klepstad et al. studied 2,201 volunteers with cancer on various opioids, including 695 of these were treated with fentanyl, and found no association with OPRM1, ABCB1, and COMT variants (as well as numerous other genes) and opioid requirements [78]. A small study on 60 Asian patients with cancer were treated with transdermal fentanyl reported to show greater-intensity central adverse events for patients homozygous for CYP3A5*3 when compared with patients with *1/*1 and *1/*3 genotypes [79]. the three ABCB1 variants (C1236T, G2677A/T, and C3435T), and C1236T alone was associated with response with decreased administration of medication in homozygous T/T variant [76]. However, the utility of CYP3A4/5 and ABCB1 testing to personalize fentanyl dosing is still uncertain.

Future Directions

Based on pharmacogenomic data accumulated thus far, investigators have identified a number of genetic variations in candidate genes that have modest correlations with individual variation in analgesic response and toxicity. A pharmacogenomics-based approach to pain management may allow rational of drug selection, resulting in improved treatment efficacy and toxicity profiles. However, in reality, available data supporting the use of identified genetic bio-markers in routine clinical practice to predict an individual's response to pain medication is unconvincing. Therefore, well-designed prospective studies with robust clinical end points are needed to demonstrate the utility of pharmacogenomics in pain management and to make the concept of personalized medicine a reality.

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