Pharmacogenomic Analysis Of Drugs Used In Treatment Of Colorectal Cancer

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Abstract

Pharmacogenomics is a very useful tool in current era of medical advancement as it contributes to individual profiling of each person suffering from a disease which can be lethal and requiring doses of medication unique to them. This is called individualisation of medication. But to find this unique dosage we have to first find the genes affecting the pathogenesis of that particular disease. Same is the case with Colorectal cancer (CRC) as we will study in this review. CRC treatment have been affected by various mutation in the RAF and RAS genes which are responsible. Different mutations lead to different level of sensitivity to drugs. The drugs used in colorectal cancer treatments are studied for the various aspects through which level of efficacy can be studied (mechanism of action, pharmacokinetics, toxicity) and through them we came to know about the genes which can be the cause of different genes and the different mutations in those genes which may be the reason for the different level of sensitivity to the drugs for each individual.

Keywords: Pharmacogenomics; oxaliplatin; bevacizumab; regorafenib; cetuximab

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1 Introduction (pharmacogenomics)

The pharmacogenomics is the study of the response of the genome after the drug reaction. It includes the two broad area of the science: pharmacology and genomics as the name indicates. Pharmacogenomics studies represents the drug induced response of the genome of a person (Ermak & Gennady 2015). Pharmacogenomics is a relatively recent area of research that investigates the connections between biology and drug consequences. The science of Pharmacogenomics has been used extensively in preclinical models in the pharmaceutical industry to describe the processes by which genetic polymorphisms affect drug metabolism (pharmacokinetics) and mechanism of action (pharmacodynamics). One of the most important uses of is to establish a basis for scientists to classify biological modifiers of drug reaction, effectiveness, and drug-induced side effects, allowing physicians to make the best clinical decision possible (N Al-Eitan and A Haddad, 2014).

Pharmacogenomics is a term that encompasses pharmacogenetics, genomics, and proteomics, and is often used interchangeably. Recognizing that most human drug reactions are multifactorial has contributed to the realization that personalised medication necessitates a complex consideration of causes, leading to the widespread usage of the word pharmacogenomics (Sheffield a n d Phillimore 2009). We can profile the changes in DNA in different individuals afflicted by a single disease using pharmacogenomics, and then use our knowledge of pharmacology to develop medications that are specifically appropriate for those cases. This application may be carried out on a wide scale by collecting data on these variants over a long period of time, dating back to the discovery of the field of pharmacology, and applying these observations to diseases with repeated mutations, which may be caused by a specific environment or by picking on those behaviours (Roses et al. 2000).

2. Colorectal cancer

Colorectal cancer or CRC is a condition in which there is uncontrolled growth of malignant tumour formed in the large intestine specifically in colon and rectum part.

Aging is the most important risk factor for sporadic colorectal cancer. Almost 99% of the occurrences of colorectal cancer occur in persons having age of 40 and 85 percent in those over 60. Because of population ageing and an increase in age-specific incidence, colorectal cancer cases are steadily increasing in Europe, suggesting that environmental or lifestyle factors, or both, may contribute to the disease. It is thought that lifestyle factors like obesity and processed meat consumption, as well as an inverse relationship between physical activity and fruit and vegetable consumption, are responsible for the significantly higher prevalence of colon cancer in more developed nations comparedto less developed nations. In addition to age, family history is the second most common risk factor for colorectal cancer. Familial adenomatous polyposis and hereditary non-polyposis colorectal cancer are the most common family cancer syndromes. However, they account for fewer than 5% of cases overall. A total of 10–20% of patients report a family history of colorectal cancer, but the pattern of inheritance and clinical symptoms do not match one of these well-defined syndromes (Winawer et al. 2003).

Development of CRC

The most frequent cause of colorectal cancer is dysplastic adenomatous polyps. A multistep process involves the simultaneous activation of oncogenes and the silencing of other genes that prevent tumour growth and repair DNA. As a result, the colonic epithelial cell has a selective growth advantage, which promotes the transition from normal epithelium to invasive colorectal cancer from adenomatous polyp. While sporadic malignancies are brought on by a progressive buildup of somatic genetic changes, inherited colon cancer syndromes are brought on by germline (heritable) abnormalities. Familial adenomatous polyposis coli is a dominantly hereditary condition that is brought on by a single germline mutation in the APC tumour suppressor gene. It is characterised by the growth of hundreds to thousands of adenomatous polyps in the colon, as well as the occurrence of colorectal cancer and other cancers, in the third and fourth decades of life. The syndrome shows clinically when an inherited mutation of one APC allele is followed by a second hit mutation or deletion of the second allele (Ballinger and Anggiansah 2007).

3. Drugs used in colorectal cancer treatment.

Oxaloplatin.

Oxaliplatinum, also known as Eloxatin, is a platinum-based chemotherapeutic drug of the same family as cisplatin and carboplatin. The medicine is currently being used in new promising chemotherapeutic regimens for advanced colorectal cancer therapy (Kang et al.2021).There are different types of platinum drugs, and some of them have different side effects. One type of platinum drug is called cisplatin, and it is a very effective cancer treatment. However, cisplatin has some very bad side effects, most notably kidney and gastrointestinal problems. So, scientists have come up with a new type of platinum drug, called carboplatin. Carboplatin doesn't have as many bad side effects as cisplatin, but it does have some different ones. One of the main side effects of carboplatin is that it can cause haematological problem. Newer platinum compounds are still under investigation (such as the orally active satraplatin), while other compounds such as nedaplatin and oxaliplatin have received FDA approval. Interestingly, neither cisplatin nor carboplatin show genetic cross-resistance with oxaliplatin. This is of particular importance in the treatment of colon cancer, which has been shown to be highly resistant to previous platinum analogues. Almost simultaneously, oxaliplatin has a favourable toxicity profile with an ototoxicity rate of 1% and a nephrotoxicity rate of 3%, except for rare peripheral sensory neurotoxicity. Sensory neuropathy is a condition that affects the

hands, feet, and perioral area that is exacerbated by exposure to cold These side effects are usually chronic and usually resolve 4 to 6 months after stopping treatment. (Van Glabbeke et al. 1988; De Francesco et al. 2002).

Pharmacokinetics

In the molecular structure of oxaliplatin, a platinum atom (Pt) is surrounded by a 1,2-diaminocyclohexane group (DACH) and an oxalate bidentate ligand. The trans-1- (R,R)–DACH–Pt isomer (oxaliplatin) is the most toxic stereo-isomeric form of oxalate–Pt– DACH which is formed due to the presence of DACH ligand (Kweekel et al. 2005).

Oxaliplatin is a platinum compound that has a similar chemical behavior and mode of action to other platinum compounds. The pro-drug oxaliplatin is created when the oxalate group is broken down by non-enzymatic hydrolysis and displaced from the drug, resulting in different monochloro, dichloro, and diaquo compounds. The rate of hydrolysis of platinum compounds can vary a lot, with being slower in cisplatin than oxaliplatin. Protein, RNA, and DNA all have a number of sulphur and amino groups. These groups can react with the highly reactive monochloro, dichloro, and diaquo intermediates. This process is thought to be responsible for the anti-cancer properties of Pt–DNA complexes. The initial steps in biotransformation and cellular detoxification of oxiplatin *in vivo* involves permanent binding of biomolecules including albumin, cysteine (Cys), methionine (Met), and reduced glutathione (GSH) (Kweekel et al. 2005; Allain et al. 2000).

Mechanism of action

Oxaliplatin is converted to active derivatives by displacing the labile oxalate ligand in physiological solutions in the absence of enzyme. Several reactive species are produced, including monoaquo and diaquo DACH platinum binding covalently to macromolecules leading to the formation of both inter- and intra-strand Pt-DNA crosslinks. The N7 locations of two adjacent guanines (GG), adenine-guanines (AG), and guanines are divided by an intervening nucleotide all form crosslinks (GNG). This can stop

DNA replication and transcription, which disregards the cell cycle mechanism and can be bad for the health. Oxaliplatin is known to have anticancer effects against colon cancer in living organisms. *In vitro* studies using various tumour models such as HT29 (colon, GR (mammary), and L1210 (leukaemia) have shown that this chemotherapy has stronger anti-proliferative efficacy when combined with another type of cancer medication, fluorouracil in comparison to the either chemical alone (Mehmood et al. 2014).

Toxicity

Oxaliplatin can be very harmful to hematopoietic system if taken in excess doses. It can lead to anemia, thrombocytopenia, and myelosuppression. It can cause hemolytic anemia and secondary immune thrombocytopenia during hypersensitivity reactions induced by chronic oxaliplatin therapy. The best way to avoid these problems is to stop taking oxaliplatin and manage your symptoms (Wei et al. 2020).

Pharmacogenomics

The goal of the oxaliplatin pharmacogenomics study is to understand the role of gene polymorphism in DNA repair and metabolism of the drug. It also helps to study the effect of the genes that are responsible for the peripheral sensory neuropathy (it is a major dose limiting factor) in oxaliplatin toxicity. Patients getting oxaliplatin medication can be divided into three categories: homozygous wild type, heterozygous, and heterozygous variation, based on their polymorphism. The results of pharmacogenomical analysis is based on two large scale prospective: pharmacogenomic studies TOSCA (three or six colon adjuvant) and JOIN (JFMC41-1001-C2) trial (Petrelli et al. 2021; Kanai et al. 2016). While TOSCA focused on the DNA repair and drug metabolism aspect of the study, JOIN focused on the peripheral sensory neuropathy (PSN) related SNPs which affect the dose limit in each individual due to varying level of toxicity endurance. The major SNPs involved in the TOSCA trial were polymorphisms in TS, GSTT1, GSTM1, ABCC1, ABCC2, ERCC1, MTHFR, GSTP1, XRCC1, XRCC3, and XPD. The target of TOSCA was the analysis both haematological and non-haematological toxicities in the patients. Both neurotoxicity and neutropenia were observed in the population which did not differ much from the other previous trial data.

The major SNPs involved in the JOIN trial were polymorphisms in CAMK2N1, DLEU7, FARS2, ABCG2, ACYP2, BTG4, CCNH, FOXC1, GSTP1, ITGA1, TAC1, and XRCC1. The purpose of the JOIN trials was the evaluation of the toxicity levels induced in the patients due to the effect on the gene due to polymorphisms of the above mentioned

genes. The patients divided in three categories depending on the level of PSN observed in them (grade 0/1 PSN, grade 2 PSN and grade 3 PSN). These patients were studied for association between PSN and polymorphism. After adjusting for total oxaliplatin dose, there were no significant relationships between grade 0/1 PSN, grade 2/3 PSN, or grade 3 PSN and any of the 12 SNP markers (Ruzzo et al. 2014; Kanai et al. 2016).

Bevacizumab

Vascular endothelial growth factor (VEGF) promotes survival, proliferation and migration of endothelial cell and is a powerful proangiogenic growth factor. VEGF is a crucial protein that is even expressed in tumour cells and it is an important target of anticancer therapy (Yang et al. 2018; Liu et al. 2021). In the last 20 years, metastatic colorectal cancer (mCRC) management has advanced dramatically, and survival rates have improved. Indeed, in clinical trials, the median overall survival (OS) for the patients having mCRC is now around 30 months, more than double what it was two decades ago (Van et al. 2016). Although a number of variables have led to improved clinical outcomes, the introduction of innovative biologic medicines that target either epidermal growth factor signalling or angiogenesis has been a crucial advance (Kasi et al. 2015). One of these treatments is bevacizumab which targets VEGF. Bevacizumab causing regression of existing tumour vasculature and preventing the creation new vessels by inhibiting the mechanism of VEGF and thus decreases the tumour growth by (Kim et al. 2020).

Pharmacokinetic

According to a recent study, bevacizumab binds more than 97% of serum VEGF. Platelets have been proven to take up bevacizumab, therefore serum VEGF is primarily produced from them. Bevacizumab is released at the sites of endothelial injury by platelets which delivers it at relatively high quantities to procoagulatory angiogenic tumour locations targeting the VEGF of the tumour cell. However, platelet VEGF blockade appears to play a key role in the development of significant adverse effects associated with bevacizumab treatment, such as bleeding, congestive heart failure, haemorrhage, proteinuria, hypertension, gastrointestinal perforation, and poor wound healing (Chellappan et al. 2018). For a typical female the calculated volume of the bevacizumab distribution was found to be 2.39 L which was 3.29 L for a typical male showing the value closer to the volume of the normal plasma. It was calculated by a two-compartment model using first-order elimination (D'Alessio et al. 2021; Lu et al. 2008). Bevacizumab weekly injection of 2-3 mg/kg to Cynomolgus monkeys resulted in a sustained 10–30 g/ml serum level, sufficient to decrease the activity of VEGF.

Distribution of bevacizumab was limited to the tumour vasculature having minute spread to extravascular space (Lin et al. 1999). Furthermore, the scintigraphic imaging of expression of VEGF in mouse models exhibited that the higher accumulation of bevacizumab in the tumour containing tissues in comparison to the tissues unaffected by the tumour (Stollman et al. 2008). The neonatal Fc Receptor (FcRn) is important for bevacizumab clearance. Pinocytosis transports the antibody into the endosomes of catabolic cells where the interaction to FcRn takes place. This interaction prolongs the antibody's half-life by delaying its breakdown and protecting it from systemic removal (Hardiansyah et al. 2018).

Bevacizumab clearance is predicted to be 0.207 L/day (0.188–0.226 L/day at 95 percent confidence interval). The removal of bevacizumab is affected by several factors such as gender, weight of the body, serum aspartate aminotransferase (AST), alkaline phosphatase (ALP) and serum albumin. In case of excessive body weight the elimination of bevacizumab might be lower to 30% lower for the body weight of 49 kg or higher up to 30% for the body weight greater than 114 kg than the mean value. In comparison to females, males have a 26% higher rate of bevacizumab clearance. The patients having serum albumin less than 29 g/L have 29% greater clearance rate. However, patients with ALP higher than 483 IU/L level have 23% higher clearance rate. The rate of bevacizumab clearance is around 10% lower in patient having high AST. Bevacizumab clearance is also affected by the size of the tumour (Lu et al. 2008). Patients having higher tumour load have a greater clearance rate (0.249 L/day versus 0.199 L/day) in comparison to those with a lower tumour burden. The effects of heterogeneity in the clearance, efficacy and safety of bevacizumab are not well understood (Gaudreault et al. 2001).

Action mechanism

Because the cells and tissues of cancer have higher rate of metabolism than normal cells, the requirement for nutrients and oxygen generally outstrips the supply. Due to this, these tissues are characterised by absence of enough oxygen to sustain its proper functioning which is also known as hypoxia. It is also considered as the key regulating element of angiogenesis. Under the condition of hypoxia there is occurrence of an interaction between hypoxia inducible factor (HIF) and hypoxia response element present in the VEGF gene that causes the induction of the transcription of the gene of VEGF protein (Tanimoto et al. 2003). The binding affinity of the circulating VEGF is higher for the receptors of VEGF (VEGFR-1 and VEGFR-2) as well as its co-receptors neuropilin (NRP-1 & NRP-2) (Muller et al. 1998).

These receptors, present on the surface of endothelial cells, play crucial role in the angiogenesis process by stimulating the recruitment and proliferation of the endothelial cells (Mancuso et al. 2006).

Pharmacogenomics

There is a relation between genetic heterogeneity and the response to bevacizumab treatment as well as the development of metastasis in VEGF-dependent and -independent pathways. However, the majority of existing data is focused on the relationship between

germline genetic variants and the outcome of the patient; the significance of mutations in somatic cells in prediction of bevacizumab efficiency has received less attention in past years, with only a few preliminary findings published. The investigations on innate variations have focused on the 5'- untranslated region (UTR) and the promoter region of VEGF-A.

However, the research on somatic mutations have primarily focused on the RAS/RAF/PIK3CA pathway due to the known association between angiogenesis and the activation of v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) signalling pathway. Fiala et al. (2016) have found that the KRAS G12A/V mutant is an important interpreter of lower progression free survival (PFS) and OS when compared to wild-type KRAS mutant and other mutations of KRAS in an enormous group of 404 metastatic colorectal cancer Caucasian patients undergoing bevacizumab therapy. In Asian mCRC patients, alterations in EGFR pathway genes were found to have a negative impact on bevacizumab effectiveness. Nakayama et al. (2017) investigated the importance of tumour mutations of RAS/BRAF/PIK3CA in patients who were given first-line bevacizumab treatment, and found that mutant-type tumours have a decreased objective response rate (ORR) than wild-type tumours, and the differences are larger when mutations are only in KRAS exon 2 and are considered not the RAS/PIK3CA/BRAF alterations. Furthermore, RAS and BRAF mutations, as well as clinicopathological characteristics, were found to be independent unfavourable predictors for disease progression in multivariate analysis. Despite the fact that these differences were not significant statistically, likely due to the minor cause mutations of RAS and the scarcity of

BRAF mutations, RAS /BRAF/PIK3CA type seem to be a viable option for identifying tumours that will react to anti-VEGF therapy. Study demonstrated that there is no link between mutational status of RAS and efficacy of bevacizumab. However, this research was conducted on a small sample size, and only a subset of patients with n

= 35 were supplemented with bevacizumab regimens. These preliminary data suggest that alterations of the genes of EGFR pathway, particularly KRAS exon 2 mutant status, may serve as possible predictive indicators for bevacizumab-targeted therapy and may aid in the selection of individuals who will benefit clinically due to bevacizumab administration (Bignucolo et al. 2017).

Toxicity

The patients administered with bevacizumab (Avastin) showed adverse effects such as hypertension, headache, proteinuria, skin related ailments that include dry skin and dermatitis, back pain, change in taste etc. These are the most prevalent adverse effects observed in patients at a rate of 10 percent and below (Singh et al. 2022). Experiments were performed in which Cynomolgus monkeys were administered with bevacizumab with dosage level which varied from 0.4 times to 20 times which is given to a human on a weekly basis. This experiment revealed that the monkeys suffered from general reduced skeletal development and growth, as well as impairment in fertility in female monkeys and reduced wound healing ability. Experiments regarding bevacizumab toxicity was also performed on rabbits. They also showed reduced healing capacity which was due to reduction in tensile strength of wound, decrease in granulation and re-epithelialization (Al-Jandan, B. 2019)

Cetuximab

In 1995, the cetuximab, an EGFR-targeting monoclonal antibody, with promising preclinical results was discovered. It is a chimeric immunoglobulin G (IgG) antibody which causes internalization and destruction of EGFR after coupling with its extracellular domain. Cetuximab was approved by FDA for metastatic CRC in 2004. This was contributed by BOND study which demonstrated the promising role of cetuximab for the improvement of progression-free survival in individuals exhibiting low response for the single-agent IRI treatment. Furthermore, cetuximab therapy extended OS and PFS in patients having CRCs when prior therapies involving fluoropyrimidine, IRI, or OX was either failed or contraindicated. Cetuximab in combination with other chemotherapies also showed encouraging outcomes (Xie et al. 2020). The general characteristics of cetuximab have been shown in Table 4.

Pharmacokinetics

The pharmacokinetics of ERBITUX are not linear, regardless of whether it is given alone or in conjunction with chemotherapy. Although the cetuximab elimination was dropped from 0.08 L/h/m^2 to 0.02 L/h/m^2 reaching to a plateau at dosage level of >200 mg/m^2. When the doses of cetuximab was increases from 20 mg/m^2 to 200 mg/m^2, the area under the concentration-time curve was found to be increased more than dosage proportionally (Daverede & Swinson 2012). The distribution volume of cetuximab was dose-independent, matching 2–3 L/meter square of vascular space. The concentrationof cetuximab attained a steady-state by the infusion of 168 mg/mL to 235 mg/mL and
41 mg/mL to 85 mg/mL, respectively three time in a week following the 400 mg/m^2 initial dose and 250 mg/m^2 of weekly dose. The half-life of cetuximab is around 112 h (63 to 230 h) (Guimond et al. 2022). There was no effect of age, gender, race, hepatic or

renal function on cetuximab's pharmacokinetics (Krens et al. 2018). Cetuximab clearance increased 1.8-fold when body surface area increased from 1.3 m^2 to 2.3 m^2, which is commensurate with the approved dose of cetuximab on a mg/m^2 basis.

Mechanism of action

Cetuximab binds with the epidermal growth factor receptor (EGFR) which belongs to the ErbB family and because of that it competes with EGF as well as other ligands for the binding. EGFR exists in monomeric for while bound to EGF or transforming growth factor-alpha (TGF-alpha) however, it forms homodimeric or heterodimeric structure when binds with other receptors of ErbB family. Dimerization of EGFR lead to the activation of its intracellular tyrosine kinase domain which causes the autophosphorylation and beginning of the cascade of intracellular events. The signalling pathway associated with EGFR regulates the proliferation, migration, differentiation, angiogenesis and death of the cancer cells. The binding affinity and specificity of the cetuximab is higher for the EGFR in comparison to the epidermal growth factor or TGF-alpha which causing ligand-induced phosphorylation and inhibition of EGFR. In experimental settings, cetuximab treatment augments the effectiveness of the irinotecan and radiation. A minor G-protein K-ras which is present downstream of EGFR is a crucial component of the EGFR signalling cascade. An activating mutation in the exon 2 of the K-ras leads to the disconnection of the pathway from the EGFR activity resulting ineffective inhibitors of EGFR (Agarwal et al. 2019; Gurdal et al. 2019; Park et al. 2019).

Pharmacogenomics

The aim of the pharmacogenomics research is to optimize the anti-EGFR treatment including cetuximab, panitumumab etc. focusing mainly on the somatic variant of the RAS (i.e., KRAS, NRAS) and RAF (i.e., BRAF) pathways. The result of this study include several therapeutically meaningful and significant findings. The mutation in KRAS gene has been recognized as the crucial factor for determining the EGFR inhibitors response hence before starting the cetuximab-based therapy it is recommended to perform KRAS genotyping to assess the existence of potential somatic mutations which can alter the anti-tumour potential of this targeted gene therapy. The most commonly genotyped mutations in KRAS gene include mutations at codons 12 and 13 of exon 2 (Guarnaccia et al. 2018). Because these somatic variants have been linked to both primary and acquired resistance, they are

recommended and must be evaluated before the treatment. Although mutations in KRAS codons 61 of exon 3, 117, and 146 of exon 4 are not so prevalent, testing them prior to treatment is recommended, especially in tumours containing wild-type codons 12 and 13. This is performed to accurately predict the response of anti-EGFR treatments. BRAF somatic mutations are no to common in CRC samples and present in 4-15% of individuals.

However, they can act as a potential markers of resistance for anti-EGFR therapy as RAF pathways if known to be involved in intracellular signalling by stimulating the MEK-ERK axis to promote the cell growth and differentiation. The BRAF V600E mutation (rs113488022) in exon 15 occurs in 8-10% of colorectal cancers and mutually exclusive with KRAS mutations (MSI). It is associated with the aggressive phenotype of tumour, microsatellite instability and lymph node metastasis. Several meta-analyses have so far considered mutational status within RAS and RAF family genes, demonstrating an associationbetween the mutant form and poor response to anti-EGFR mAbs (cetuximab and panitumumab) and the development of acquired resistance for these therapies. Furthermore, the presence of somatic mutations in downstream genes of the EGFR cascade have been suggested as a predictor of anti-EGFR mAb sensitivity. The pathways including RAS-RAF-MAPK and phosphoinositide-3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) regulate the proliferation, angiogenesis and migration of the tumour. Analysis of these pathways has been revealed the existence of somatic mutations in the PTEN, NRAS, and PIK3CA genes which can act as a potential marker for the anti-EGFR effectiveness particularly in tumours containing mutation in EGFR gene. Several uncommon mutations present in codons 12, 13, 61, 117, and 146 of the exon 2-4 of NRAS gene are associated with the intrinsic tumour tolerance and reduced ORR, PFS, and OS which implies that the genotyping should be performed before the therapy and also afterwards. Based on the research, along with the EGFR downstream cascade, missense somatic mutations in genes encoding the drug-target EGFR are linked with the resistance acquired to anti-EGFR mAbs. Thus assessment of these genes is also necessary during the treatment for the optimization of patient care. These findings suggest that multiple tumour alterations occurring in pathway related to cetuximab must be considered when establishing the administration of medication. mutational status of KRAS is the only biomarker commonly examined in the clinical environment, but its conjunction with other somatic drivers of response to cetuximab response and/or acquired resistance should be studied to optimise anti-EGFR treatment even further (Bignucolo et al. 2017).

Toxicity

Cetuximab toxicity leads to the cardiopulmonary arrest and/or quick mortality in 2% of individuals. In clinical investigations, serious infusion reactions occurred in roughly 3% of people who received cetuximab, with fatal outcomes in less than 1 in 1000 cases. If a significant infusion response occurs, cease the cetuximab administration immediately and completely. Before treatment, IgE antibodies which developed against cetuximab were found in the serum of the majority of people who had a hypersensitive reaction to the drug. In mouse cell line the antibodies developed against galactose-α- 1,3-galactose which is associated with the formation of cetuximab (Bardash et al. 2019).The EGFR receptor blocking causes an acne-like or maculopapular rash which is included as its most common side effect. Acneiform rash has been reported in 76-88% of patients (severe in 1 to 17%) which develops within first week of the drug administration and require modification of dose and get resolved after stopping the treatment in most of the patients. Hypomagnesemia is a prevalent condition and may get severe. EGFR blocking may cause magnesium transport to be disrupted as EGFR is over- expressed in the ascending limb of the Henle loop of the kidney where the absorption of the 70% of the filtered Mg occurs. Under the conditions of the fatigue or hypocalcemia which arises after the cetuximab treatment, blood magnesium levels should be monitored and replenished when needed, because symptoms may improve quickly with supplementation (Park et al. 2019).

Conclusion

Pharmacogenomics study of the drugs studied in this review included their mechanismof action and especially the interaction of the drugs with the target molecule with which they bind to. It either leads to inhibition mechanism leading to reduction of the tumour size (angiogenesis) or attack on the cell repair mechanism of the tumour developed leading to apoptosis. Drugs such as Oxaliplatin are highly dependent on the DNA repair and drug metabolism to show their effectivity. Hence any sort of polymorphism which affect the genes related them is suspected to affect the efficacy of the drug. There is also the case of the major toxicity of oxaliplatin, peripheral sensory neuropathy, which acts as a dose limiting factor as ovedosage may make PSN permanent and non-recoverable. So the genes which may be the cause of hypersensitivity were also studied. There weren't any solid evidences obtained from the studies covered in the review which may give a strong suggestion to these polymorphisms affecting the drug affect in thepatients.

The anti-angiogenic drugs such as cetuximab, panitumumab, bevacizumab and regorafenib

are dependent on the molecules which are responsible for angiogenesis and formation of solid tumor. Mutations in the genes which are responsible for the production of these molecules are suspected to affect the activity of these drugs. So far different trials showed different results.

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