Original article

Exonic variants in multiple myeloma patients associated with relapsed/refractory and response to bortezomib regimens

Ashraf Kakoo*, Mustafa Al-Attar, Taban Rasheed

Department- College of Science, Salahaddin University, Erbil, Iraq

A R T I C L E   I N F O

Article history:
Received 3 May 2021
Revised 8 September 2021
Accepted 9 September 2021
Available online 16 September 2021

Keyword:
Multiple myeloma
drug resistance
Next-generation sequencing

A B S T R A C T

Novel treatment in multiple myeloma represented by proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies have produced a deep response. However, relapses are possible, and all classes of drugs are refractory to patients. Next-generation sequencing has improved our understanding of the multiple myeloma genome related to drug resistance and has discovered many genomic variants. Therefore, this study was conducted to investigate new variants associated with drug resistance in MM patients who relapsed and refractory to bortezomib regimen and daratumumab treatment using next-generation sequencing for whole-exome sequencing. Peripheral blood samples were collected in EDTA tubes from six patients; four were in relapsed and refractory to bortezomib regimens and daratumumab; two patients responded to bortezomib regimens. Whole-exome sequencing was performed by the MGI-DNBSEQ-G400 instrument. We identified 21 variants in multiple myeloma patients. Seventeen variants were found in relapsed and refractory multiple myeloma in 11 genes (GNAQ, PMS1, CREB1, NSUNS2, PIK3CG, ROS1, PMS2, FIT4, KDM5A, STK11 and ZFHX3). And four variants were identified in two patients with response to bortezomib regimens in 4 genes (RAF1, CREB1, ZFHX3 and INSR). We have observed several genetic variants in many genes that may have been associated with the poor prognosis and poor response to treatment in these patients. These values should be further confirmed in large sample studies using the RNA-seq technique to identify genome expression.

1. Introduction

Multiple Myeloma (MM) is a plasma clonal cell cancer, is distinguished by widespread genomic heterogeneity. As a result, there is a difference in drug response and disease progression (Gupta et al., 2015; Lohr et al., 2014). The novel treatments like proteasome inhibitors, immunomodulatory, and monoclonal antibodies have increased MM patients’ survival. However, MM remains irremediable cancer. Most MM patients die of their disease acquired drug resistance limits current therapies’ efficacy (Kumar and Rajkumar, 2014).

Bortezomib (Velcade) was the first class of proteasome inhibitors show an effect against MM. It works by blocking activations of the 20S core of the proteasome, which induces apoptosis in myeloma as well as lymphoma cells (Mohan et al., 2017; Ri, 2016). The U.S. FDA approved Daratumumab in 2015 for MM patients, a monoclonal antibody (IgG1) that targets CD38, which has highly expressed in myeloma cells (Nahi et al., 2019).

Next-generation sequencing (NGS) is a method that can sequence millions of fragments of DNA or complementary DNA simultaneously. It has been quickly accepted in the clinical and molecular laboratory due to its capacity to simultaneously analyze many genes or gene regions with a single test compared to traditional methods (Yohe and Thyagarajan, 2017).
fundamental molecular events that underlie MM’s growth and anticancer drug resistance mechanism.

An effective way to understand cancer’s molecular basis is to sequence the entire genome or the protein-coding exome by Next-generation sequence (NGS) (Chapman et al., 2011; Zhao et al., 2019). Single nucleotide polymorphisms (SNP) are among the most common forms of genetic variations in the human genome. SNPs in genes that regulate the cell cycle, DNA mismatch repair, metabolism and immunity are connected with genetic susceptibility to cancer (Schirmer et al., 2016). To understand the molecular pathogenesis of different cancers, knowing the mechanisms underlying the effects of SNPs that result in cancer susceptibility is essential. From a clinical viewpoint, SNPs are therapeutic biomarkers and potential diagnostic (Deng et al., 2017).

In this study, we performed whole-exome sequencing (WES) in MM patients who were relapsed and refractory to bortezomib regimen and daratumumab treatment for the discovery of new variants related to drug resistance by using next-generation sequencing.

2. Materials and methods

2.1. Sample collection

The current study was authorized and approved by the Human Ethics Committee of the College of Science, Salahaddin University, Erbil (Approval No: 3/2/2002 Date: 9/6/2019). All patients provided written, informed consent for the publication of data in this study. This study was conducted from August 2019 to June 2020 in Nanakali Hospital for Blood Diseases and Cancers, Erbil City. Peripheral blood samples were collected in an EDTA tube from six patients; four blood samples were taken in relapsed and refractory to proteasome inhibitors (bortezomib), immunomodulatory drugs (thalidomide) and monoclonal antibodies (Daratumumab), and two patients had a response to bortezomib regimens.

2.2. DNA extraction and library preparation

QiAamp DNA blood kit (QIAGEN) was used to isolate DNA from peripheral leukocytes, following the manufactures protocol. Twist Human Core Exome Enzymatic Fragmentation (EF) Multiplex Complete kit was used for library construction, and MGIEasy FS DNA Library Prep Kit was performed for formation circular DNA and the library to be ready for sequencing on the MGI system.

2.3. Sequencing and bioinformatics

The library was sequenced on the(MGI-DNBSEQ-G400, China) instrument generating 150 bp paired-end read with 100X mean target coverage. The output of NGS was raw fastq files. This file was quality assessment by FastQC software. Then reads were aligned to the reference human genome (hg19) using Burrows-Wheeler Aligner (BWA) software. Variants were identified with Genome Analysis Toolkit (GATK) software. Integrative Genomic Viewer software (IGV) was used for variants visualization.

2.4. Statistical analyses

The statistical analyses were performed with the GraphPad Prism Software (version6.0). D’Agostino-Pearson omnibus test, Shapiro-Wilk normality test and Kolmogorov-Smirnov test were used to determine whether the data were normally distributed or not. Normally distributed data presented as means ± SE (Standard Error), and not normally distributed data presented as median (range).

3. Results

The patient’s demographics and baseline characteristics are summarized in Table 1. This study identified 21 variants in MM patients. 17 variants were recorded in 11genes of four patients in relapsed and refractory MM (GNAQ, PM51, CREB1, NSUNS2, PIK3CG, ROS1, PM52, FIT4, KDM5A, STK11 and ZFHX3), Table 2. And four variants were identified in two patients with response to bortezomib regimens in 4 genes (RAFI, CREB1, ZFHX3, and INSR), Table 3.

Out of 17 variants in four relapsed in refractory MM, six variants were detected in the first patient in six genes (GNAQ, PM51, CREB1, NSUNS2, PIK3CG and ROS1); all variants were SNP, except one variant was insertion (c.301-4insT) in the PM52 gene. Four variants were found in the second patient in the four genes (PIK3CG, GNAQ, FIT4, and PM52); the variants were SNP, while one variant was insertion (c.301-4insT) in the PM52 gene. Three variants were noted in the third patient in the three genes (CREB1, ROS1, and PIK3CG); the variants were SNP. And four variants were reported in the fourth patient in four genes (KDM5A, STK11, ZFHX3 and PM51); the variants were SNP, except one variant was insertion (c.7800–7801 ins AGGTCG) in the ZFHX3 gene.

Out of four variants in two patients responding to bortezomib regimens, two variants were recorded in the first patient in two genes (RAFI and CREB1); the variants were SNP. And another two variants were recorded in the second patient in two genes (ZFHX3 and INSR); the variant in the ZFHX3 gene was insertion (c.7800–7801 ins AGTGGC) and variant in the INSR gene was SNP.

4. Discussion

The introduction and advancement of new sequencing technologies have opened up new biological scenarios in the last decade, especially in the field of onco-hematologies (Reuter et al., 2015). The MM genome analysis reveals the discovery of novel targets or single pathways controlling the proliferation of myeloma cells will enhance the clinical outcome and survival of patients with refractory MM. NGS has found new insights into the complexity of the intra-clonal heterogeneity of MM. Many new genes have been detected by using NGS. However, some genes have been accepted as markers for diagnosis, prognosis, and treatment (Weaver and Tarimian, 2017). In this study, we performed WES for four patients in relapsed and refractory MM. We identified 17

| Variable | Number of patients (%) |
|----------|------------------------|
| Total number of patients | 6 |
| Age, median (range) | 64.5 (41 – 81) |
| Sex | Male (33.4%), Female (66.6%) |
| Myeloma isotype | IgG (66.6%), LCM (33.4%) |
| Laboratory values | Creatinine (mg/dl), median (range) 1.5 (2.4–1.2), Urea (mg/dl), median (range) 73.6 (110–47), B2M Microglobulin (mg/l), median (range) 8.2 (9.5–4) |
| ISS | I: 0, II: 2 (33.4%), III: 4 (66.6%) |
| Treatment | Relapsed to Vel-TD & Daratumumab 4 (66.6%), Response to Vel-TD 2 (33.4%) |

LCMM light chain MM, ISS International staging system, Vel-TD velcade (bortezomib), thalidomide and dexamethasone.
Nucleotide variants identified in patients response to bortezomib.

In particular, several lines of evidence display an increase mutation rate (Fukuhara et al., 2015).Mismatch repair (MMR) enzymes take action as proofreading complexes that preserve genomic integrity and MMR-deficient cells are predisposed to change in the amino acid, may affect the expression of these genes and affect protein function and stability. Many of these genes have been related to drug resistance pathways and cell survival in MM and many other cancers.

In Table 2, our results revealed variant likely pathogenic in the CREB1 gene in two patients; this gene is a guanine nucleotide-binding protein regulating B-cell development and survival (Jonsson et al., 2017). This variant is previously reported in a study on natural killer / T cell lymphoma patients (Li et al., 2019). A study suggests that the variation of GNAQ stimulates the nuclear factor kappa B (NF-κB) pathway in cancer, which increases receptor activator of nuclear factors-xB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) expression (Choi et al., 2020). It has been suggested that activating the NF-κB pathway is essential in MM's pathogenesis and resistance to treatments (Ikeda et al., 2011). Several factors associated with the growth and survival of MM cells related to CREB family members have been identified (Zhang and Fenton, 2002). A variant likely pathogenic in the PMS1 gene was observed in one patient, which is a splice nonsense variant. PMS1 is a tumour suppressor gene. Such a null variant most probably cause a loss of function mutation. Nonetheless, variant unknown significant (VUS) in the PMS1 gene in two patients; this is a splice site variant. Human Splicing Finder predicts this variant as likely pathogenic. PMS2 gene is a tumour suppressor such a splice site variants most probably cause a loss of function mutation. PMS1 and PMS2 genes are mismatch repair system components. DNA mismatch repair (MMR) enzymes take action as proofreading complexes that preserve genomic integrity and MMR-deficient cells display an increase mutation rate (Fukuhara et al., 2015). MMR is one of the main biological pathways implicated in cancer development and drug resistance (Torgovnick and Schumacher, 2015). The change of DNA repair pathways can enhance tumorigenesis and can induce drug resistance. In particular, several lines of evidence confirm the strong connection between DNA damage repair mechanisms and response to treatment in MM and patients’ survival (Walker et al., 2015a; Kasambahara et al., 2014). Mice that have the PMS2 gene deleted develop lymphomas (Chen et al., 2005).

Additionally, we found VUS in the CREB1 gene in two patients. There is no data found about this variant and its functional effect. Cyclic AMP Response Element Binding (CREB) protein is a transcription factor having a major role in the nuclear responses to various external signals that lead to differentiation, proliferation, survival and apoptosis (Dauria and Di, 2013). Knockdown of CREB1 significantly inhibits cell proliferation, colony formation, migration and invasion in addition to induced cell arrest at G1/G0 phase in vitro. Many genome-wide association studies have shown that the number of putative target genes for CREB is around 5000 (Sakamoto and Frank, 2009; Mayr and Montminy, 2001). Previous studies have shown that CREB is a proto-oncogene which overexpression promotes cellular proliferation, in haematopoietic cells (Sassone-Corsi, 1995; Montminy, 1997). In vitro and in vivo abnormal proliferation and survival of myeloid cells appear due to the upregulation of CREB target genes such as CyclinA1 (Cho et al., 2011). Several factors associated with the growth and survival of MM cells related to CREB family members have been identified (Zhang and Fenton, 2002), like the myeloid cell leukaemia-1 (MCL-1) protein and an anti-apoptotic member of the B-cell lymphoma 2 (BCL-2) family. These have been considered critical regulators of MM cell survival and suggested an attractive therapeutic target (Zhang and Fenton, 2002).

Furthermore, VUS in the NSUN2 gene was recorded in one patient. This gene's effect on cancer mechanism is epigenetic; no medical record exists about this variant. NOP2/Sun RNA methyltransferase family member 2 (NSUN2) encoded by this gene. This enzyme catalyzes the methylation of cytosine to 5-methylcytosine of intron-containing RNA precursor. This is an essential step in pairing anticodon-codon, and therefore crucial for proper messenger RNA translation (Blanco and Frye, 2014). In addition, this modulation plays a vital role in tissue homeostasis, cell division. Increase the production of protein by various mechanisms such as promoting mRNA stability and enhancing protein synthesis and translation (Chellamuthu and Gray, 2020). The alterations to NSUN2 are common in breast cancer (Manning et al., 2020), colon cancer (Okamoto et al., 2012), and lung cancer.

### Table 2

| Patients No | Gene names | Variants coordinate | Amino acid change | Zygosity | Variants classification |
|-------------|------------|---------------------|-------------------|----------|------------------------|
| 1           | GNAQ       | NM_0020725.5: c.286A > T | p.Thr96Ser        | Heterozygote | Likely pathogenic     |
|             | PMS2       | NM_001322009.9: c.301-4insT | ————             | Heterozygote | Unknown significant     |
|             | CREB1      | NM_134442.5: c.179A > T | p.Asn608le        | Heterozygote | Unknown significant     |
|             | NSUN2      | NM_017755.6: c.718A > C | p.Asn240His       | Heterozygote | Unknown significant     |
|             | Pik3cg     | NM_002649.3: c.2174G > C | p.Gly725Ala       | Heterozygote | Unknown significant     |
|             | Ros1       | NM_002944.2: c.5100C > A | p.Tyr1700Ter      | Heterozygote | Unknown significant     |
| 2           | Pik3cg     | NM_002649.3: c.2174G > C | p.Gly725Ala       | Heterozygote | Unknown significant     |
|             | GNAQ       | NM_0020725.5: c.286A > T | p.Thr965er        | Heterozygote | Likely pathogenic     |
|             | Fli1       | NM_001354989.2: c.3919T > C | p.Ter1307Argext   | Homozygote | Unknown significant     |
|             | PMS2       | NM_001322009.9: c.301-4insT | ————             | Heterozygote | Unknown significant     |
|             | CREB1      | NM_134442.5: c.179A > T | p.Asn608le        | Heterozygote | Unknown significant     |
|             | Ros1       | NM_002944.2: c.5100A > T | p.Try1700Ter      | Heterozygote | Unknown significant     |
|             | Pik3cg     | NM_002649.3: c.2174G > C | p.Gly725Ala       | Heterozygote | Unknown significant     |
| 3           | Kdm5a      | NM_001042603.3: c.3235G > A | ————             | Heterozygote | Unknown significant     |
|             | Stk11      | NM_000453.5: c.1150C > T | p.Asp1079Asn      | Heterozygote | Unknown significant     |
|             | Zfhx3      | NM_001164766: c.7800-7801 ins ACTG GCC | ————             | Homozygote | Unknown significant     |
|             | Pms1       | NM_000535.5c.1627G > T | p.Glu543Ter       | Heterozygote | Likely pathogenic     |

| Patients No | Gene names | Variants coordinate | Amino acid change | Zygosity | Variants classification |
|-------------|------------|---------------------|-------------------|----------|------------------------|
| 1           | Raf1       | NM_002880.3: c.1516A > G | p.Thr506Ala      | Heterozygote | Unknown significant     |
|             | Creb1      | NM_134442.5: c.179A > T | p.Asn608le        | Heterozygote | Unknown significant     |
| 2           | Zfhx3      | NM_001164766: c.7800-7801 ins ACTG GCC | ————             | Homozygote | Unknown significant     |
|             | Insr       | NM_001079817: c.653-5ins TC | ————             | Heterozygote | Unknown significant     |
We identified two unknown variants in two genes of tyrosine kinases receptors (RTKs), the FLT4 gene in one patient and the ROS1 gene in two patients. In various stages of neoplastic growth and progression, RTKs are involved. Their signalling affects cell growth, adhesion, differentiation, motility and death (Berenson et al., 2015; Robinson et al., 2000). When subverted, these processes may give origin to cancer (Blume-Jensen and Hunter, 2001). Fms-related tyrosine kinase 4 (FLT4) is a member of class III receptor tyrosine kinases, including vascular endothelial growth factors receptors (VEGF-C). Silent mutations, nonsense mutations, missense mutations, and frameshift deletions in the FLT4 gene are detected in cancers like stomach, intestinal, and skin cancer (Mendes Oliveira et al., 2018; Melikhov-Rezvini et al., 2015). ROS1 (ROS proto-oncogene1, receptor tyrosine kinase) is a gene that encodes the proto-oncogene tyrosine-protein kinase ROS protein. The rearrangement of this gene is detected in lung adenocarcinoma, breast invasive ductal carcinoma, cholangiocarcinoma, gastric, ovaries, and colorectal cancer (Lin and Shaw, 2017), as well as ROS1 fusions have been recorded in MM (Morgan et al., 2018). This missense variant in these genes and altered amino acid may affect protein function or stability, and there is no data about these variants.

Whole exome sequencing revealed a missense variant in the PIK3CG gene (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit gamma) in three patients. Missense variant may cause loss or gain of function. PIK3CG is a tumour suppressor gene (Samuels and Ericson, 2006; Li et al., 2015) and lipid kinases family that integrates cues from cytokines, growth factors and other environmental signals, then translating them to intracellular signals that regulate various signalling pathways (Thorpe et al., 2014). These pathways regulate many cellular processes and physiological functions, including cell proliferation, metabolism, growth, survival and motility (Vanhaesebroeck et al., 2010). This pathway has been shown to be constitutively activated in MM cells and to have a pleiotropic effect influencing drug resistance, angiogenesis, proliferation, and cell adhesion (Sahin et al., 2014).

A missense variant in the Lysine(k)-specific demethylase 5A (KDM5A) gene was detected in one patient. This gene encodes a protein that acts as gene regulation by eliminating di-and tri-methyl marks from lysine four on histone H3, making them potential players in tumour suppressors’ downregulation. Still, it can also report that their action represses oncogenes. Depending on the methylation site, their effect on transcription may either suppress or activate (Pich et al., 2019). Histone methylation is essential in regulating gene expression, and its dysregulation has been detected in many cancers (Højfeldt et al., 2013). It has been suggested that the KDM5 family of demethylases have a role in drug tolerance (Pich et al., 2019). Upregulation of this gene is associated with chemotherapy resistance detected in gastric cancer (Li et al., 2014), lung cancer (Teng et al., 2013) and breast cancer (Hou et al., 2012). Moreover, Whole-exome sequencing revealed a missense variant in the serine/threonine kinase11 (STK11) gene in one patient, VUS. This gene encodes a protein that belongs to the serine/threonine kinase family. The protein functions in the regulation of cell polarity, apoptosis, DNA damage repair (Li et al., 2020b). Recently STK11 gene has been identified as a tumour suppressor gene, which often is silenced in the wide spectrum of truncating mutation (Li et al., 2020b).

Finally, VUS in the zinc-finger homeobox 3 (ZFHX3) was found in one patient. This gene is a large transcription factor containing four homeodomains, 23 zinc-finger domains, and many other motifs (Hu et al., 2019). This is a splice site variant. Human Splicing Finder predicts this variant as likely pathogenic. This gene is detected as a tumour suppressor in several cancers (Walker et al., 2015b). Such splice site variants most probably cause loss of function mutation.

As part of this study in Table 3, we performed WES for two patients in response to bortezomib regimens, and we identified four variants in 4 genes (RAFI, CREBI, ZFHX3, and INSR). Two variants in two genes (CREBI and ZFHX3) were recorded in relapsed and refractory MM patients. VUS in the RAF1 gene was detected. Such a missense variant may cause loss or gain of function. RAF1 is a proto-oncogene, serine/threonine kinase that encoded a protein is a mitogen activated protein kinase (MAPK) that functions downstream of small GTPase (RAS) and activates mitogen activated protein kinase kinase 1/2 (MEK1) and (MEK2) (Li et al., 2020a). In several cellular processes, the MAPK pathway is critically involved. The dysregulation of this pathway leads to uncontrolled cellular proliferation, survival, and dedifferentiation. Consequently, the MAPK pathway is changed or inappropriately activated in most cancers (Yaeger and Corcoran, 2019). A splice site variant in the Insulin Receptor gene (INSR) was recorded; this variant was VUS. The insulin receptor, a tyrosine kinase protein, is encoded by the INSR gene. This splice site variant may cause loss or gain of function. The insulin receptor is overexpressed in some malignancies, affecting abnormal response to proinsulin, insulin, and insulin-like growth factors, with predominant mitogenic rather than metabolic effects. The biological function of the overexpressed insulin receptor in cancer is not yet well understood (Vella et al., 2018).

In this study, the genes that recorded genetic change in relapsed and refractory MM patients may have a critical role in tumour progression and drug resistance like GNAQ, PMS1, PMS2, PIK3CG and KDM5A. Variation in these genes may affect the expression of genes and affect coding protein.

In conclusion, we detected several genetic alterations in many genes (GNAQ, PMS1, CREBI, NSUNS2, PIK3CG, ROS1, PMS2, FIT4, KDM5A, STK11 and ZFHX3). These variants lead to change in the amino acid, may affect the expression of these genes and affect protein function and stability. That may have been associated with the poor prognosis and poor response to treatment in these patients. These values should be further confirmed in large sample studies using RNA-seq technique to identify genome expression.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the patients who participated in this study and all medical and administrative staff of Nanakuli Hospital for Blood Diseases and Cancer.

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