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MULTIPLE MYELOMA: AN UPDATED REVIEW ON THE PLASMA CELL NEOPLASM

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Abstract: A cancer is one that develops due to uncontrolled proliferation of cells in the body. While some cancers hijack the bodies at such jaw-dropping speeds that it becomes difficult to record its prognosis, such as Lung cancer or Colorectal cancer [1], some develop more slowly and take time for its symptoms to be profound, such as Multiple Myeloma. Originating from the Greek words “Myelo” meaning marrow and “oma” meaning tumor, Multiple Myeloma is an incurable hematological disease, belonging to a family of cancers called plasma cell dyscrasia [2]. Its distribution across the world varies widely with race. Its well-known prognosis involves giving rise to malignant plasma cells originating from the post-germinal centers of B cells in the lymphoid organ, which spread from the bone marrow of one bone to the rest of the bones in the body. It is also characterized by heightened monoclonal antibody production. Malignant plasma cells do not have the ability to correctly produce antibodies. An antibody consists of 2 heavy chains of either IgA,IgM,IgG,IgE or IgD type and 2 light chains of either kappa or lambda type. Mutations in plasma cells lead to incorrect bonding of the heavy and light chains of the antibody, and in some cases, bonding does not even take place; which leads to free light chains entering into the bloodstream [3], the level of which is a significant diagnosis factor for Multiple Myeloma. In addition, abnormal plasma cells also release M proteins, or Myeloma proteins, which have no use for the body, apart from serving as an indication for the presence of Multiple Myeloma. Delayed diagnosis of this cancer is one of the common causes of inability to cure it. However, if the disease is caught during early stages, the patient’s survival rate may be increased with the right treatment.

Keywords: Myeloma; Plasma cell; Antibody, Mutation; Oncogene; Autologous stem cell therapy; Combination Therapies.

1. Introduction

Cases of Multiple Myeloma (MM) have been recorded for over two centuries. Yet, the origin of this cancer, still remains a mystery. Hence this article strives to provide a comprehensive review of the potential sources of Multiple Myeloma and its prognosis, while also running through the recent advancements in its treatment. This article also explains the new criteria for MM diagnosis, which has a direct impact on MM patient survival rates.

2. Epidemiology

2.1 Distribution of Multiple Myeloma globally

According to the statistics published in an NCBI article [4], Multiple Myeloma cases across the globe gained peak between the years 1990 and 2016. Analysis of data showed that the most affected regions included East Asia and Latin America, as shown as Fig 1. Countries such as Taiwan, North Korea and China were estimated to have gained a whopping 262% increase in the number of MM cases [5]. Although concrete studies of MM cases in the Asian continent have not been made, it is assumed that the rise in cases could be narrowed down to increased life expectancy, combined with rapid industrialization [6]. As for Latin America [7], lack of access to proper diagnosis and treatment led to their deteriorating condition. In fact, most developing countries face the problem of unavailability to cancer therapy, such as Stem Cell Therapy [8], that increase chances of survival by at least 30%. Broadly, the distribution of MM globally is highly disparate; the reason of which could be brought down to genetic susceptibility in various oncogene groups [9].

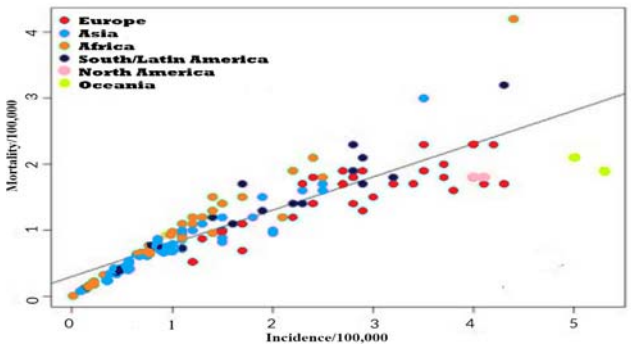

Fig 1: *Graph relating Mortality with Incidence of MM cases at a global level.*

2.2 Multiple Myeloma in India

The incidence of Multiple Myeloma compared to other cancers, in India is 1.19% [10]. Of this, the affected male to female ratio was estimated to be 59:41. Clearly, men had the higher proportion of MM cases. Digging deeper, this disparity can be traced back to the origin of a myeloma cell; the gain of odd-numbered chromosomes, leading to a mutation called Hyperdiploidy. The rate of Hyperdiploidy occurring in men is recorded to be 62%, while only 50% cases in women were recorded for the same. The relatively high proportion of women developing Multiple Myeloma is due to the IGH translocation of chromosome 14 of plasma cells. Hence, it can be understood and concluded that men and women have different origins of development of Multiple Myeloma. Region wise, Southern India [11] is recorded to have been affected the most, followed by the Northern regions [12].

3. Etiology

Every cancer begins with a specific type of mutation occurring in the proto-oncogenes and tumor suppressor genes in the DNA of a specific cell. In Multiple Myeloma, the affected cell is a plasma cell [13], responsible for producing antibodies.

3.1 Multiple Myeloma at the Gene level

During mutation, the proto-oncogenes turn into oncogenes, which lose control over the regulation of cell division, leading to uncontrolled cell proliferation.

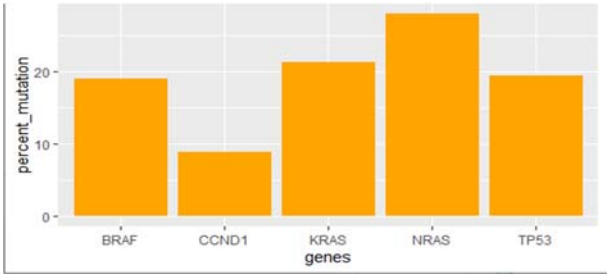

Fig 2: *Percentage of mutation vs the gene*

The above genes are usually associated with various pathways such as RNA processing and protein translation. The mutations identified in the variants of all these genes were missense, according to the same study, which was conducted using Next Generation Sequencing (NGS) techniques. Now let's review each mutated gene. The NRAS gene is a proto-oncogene, belonging to the family of Ras genes that code for proteins that have GTPase activity. It is mapped on chromosome 1. Essentially, this protein hydrolyses the nucleotide, Guanosine Triphosphate, into Guanosine Diphosphate, which is responsible for binding with the alpha-subunit of G-protein, which keeps the GPCR (the receptor that binds with extracellular ligands to relay messages) on the cell surface, in its resting state. Other genes belonging to the Ras family are KRAS and HRAS. As is the case with any gene mutation, mistakes in copying the DNA during cell replication, environmental factors such as exposure to UV light and chemicals, cause mutations in the gene, which subsequently codes for different proteins. The mutated Ras proteins can be identified by the switch in amino acid bases at the G12, G13 and Q61 positions in the G protein.

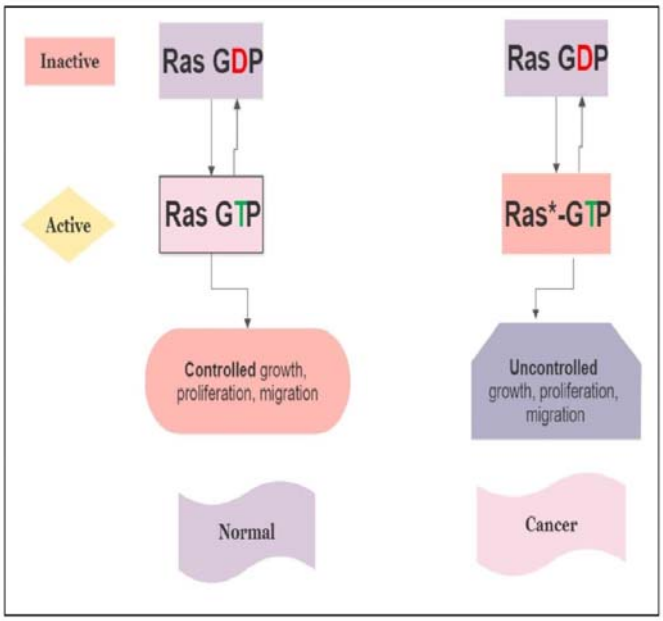

Fig 3: *Mechanism of Ras mutation. Data obtained from [14]*

The gene next in line contributing to Multiple Myeloma is the BRAF gene. Mutations involving this gene occur at the 600th amino acid position, where glutamic acid substitutes valine [15, 16]. It is also called the BRAF V600E mutation [17]. The TP53 gene's mutations are rarely detected during diagnosis of Multiple Myeloma [18], but they become more apparent during advanced stages of the cancer [19]. The results from a study published in [18, 20] showed that the mutated TP53 gene underwent del(17p), that is deletion of the p arm of the 17th chromosome. CCND1 gene encodes the Cyclin D1 protein [21]. It is mapped to the q arm of chromosome 11. Excessive transcription of Cyclin D1 through RAS-mediated pathways blocks its proteolysis, which results in oncogenesis [22]. It is noteworthy to mention that the above mutations are all acquired only; none inherited.

3.2 *Relation with Age*

Age can be pinned down as one of the most important deciding factors for increase in MM risk. Older patients of ages above 60 years [23], are most affected by Multiple Myeloma, and also have much decreased survival rates compared to a MM patient below the age of 45 years. This can be explained as follows: The precursor to MM, called Smouldering Multiple Myeloma, or SMM, is a rather asymptomatic condition, and therefore may not be diagnosed early [24]. The chance of SMM developing into MM largely depends on a few key conditions that the patient has a high risk of developing, such as Osteoporosis and Pneumonia [25]. The above two conditions pose as high-risk factors only in senior age categories (above 55 years), because of which, the chance of developing a more aggressive form of MM is higher for them.

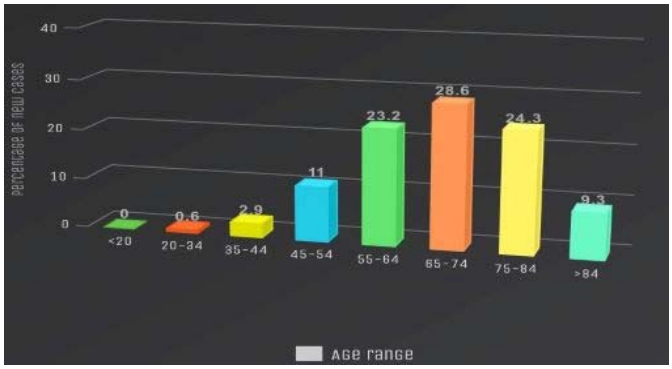

Fig 4: *Percentage of new cases vs age range*

3.3 *Relation with Environmental Factors*

3.3.1 *Benzene*

An important solvent used in various industries to produce rubber, gum, resins, fats, pharmaceuticals and many more [26], benzene proves to be carcinogenic to specific organs, including the bone marrow. Benzene may enter the body either through the lungs, the gastrointestinal tract or even through the skin. Penetration of benzene into the bone marrow results in the production of malignant plasma cells [27]. Benzene is also present in cigarette smoke, which makes smokers 10 times more vulnerable to Multiple Myeloma [28]. Reports of overexposure to benzene, causing Multiple Myeloma, have been recorded since the 1960s. While some studies confirm that Benzene has a direct effect on plasma cells, some other studies categorize benzene only as a risk-factor [29]. Studies proved that metabolites of benzene create more harm than benzene itself. In the *body,* benzene gets metabolized in the lungs first, and then secondary metabolism takes place in the bone marrow.

(a) Mechanism:

The mechanism by which benzene is metabolized sequentially can be explained briefly through the following steps: (i) Benzene undergoes oxidation in the liver and lungs to give benzene oxide; (ii) A major amount of this benzene oxide rearranges to phenol, while the remaining amount undergoes hydrolysis to produce catechol and 1,2-benzoquinone; (iii) Phenol may either be excreted or further metabolized to hydroquinone and 1,4-benzoquinone; (iv) Hydroquinone is catalyzed to produce a reactive metabolite called 1,2,4-benzenetriol; (v) The electrophilic nature of benzene oxides makes them react with several proteins within and outside the cells, which interferes with the cells' machinery and (vi) Certain peroxidases in the bone marrow convert phenol to quinones, which directly bind with cellular molecules and interfere with their functions, thus leading to cytotoxicity [30,31].

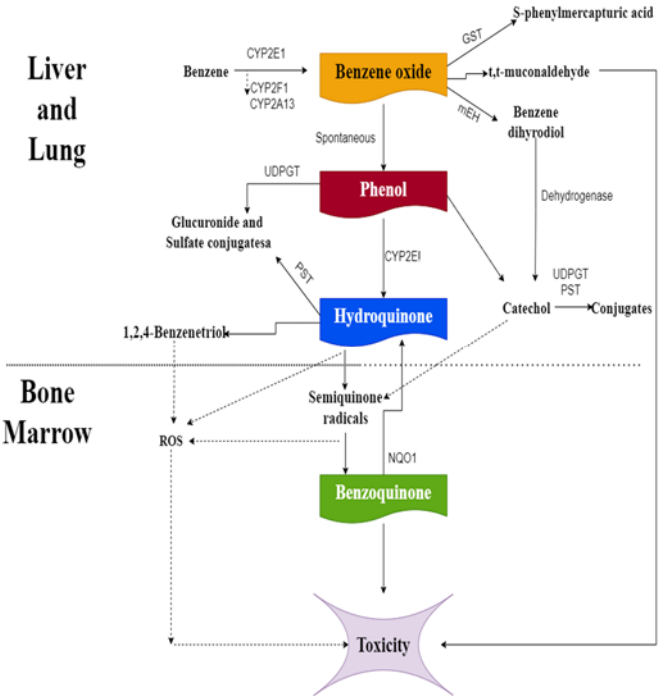

Fig 5: *Process of benzene metabolism in Humans*

3.3.2 *Dioxins:*

Dioxins are a group of aromatic compounds (chemical name 2,3,7,8-tetrachlorodibenzo-p-dioxin or TCDD), commonly existing as by-products from bleaching and pesticide industries. They come under the category of Persistent Environmental Pollutants, and

enter the body through varied sources such as fatty foods, ash from burnt household waste, or through the air we breathe. Dioxins were first linked with Multiple Myeloma through an herbicide used during war, by the US military on Vietnam, called **Agent Orange** [32]. Although a direct correlation between Agent Orange and Multiple Myeloma was not bridged, the former was linked with increase in chances of developing Monoclonal Gammopathy of Undetermined Significance or MGUS, as published by a research article in 2015 [33]. MGUS is considered a stepping stone to developing Multiple Myeloma [34], as the former is not cancerous on its own, and contributes to only less than 10% of the malignant plasma cells in the bone marrow. On an average, about 1% of people with MGUS go on to develop multiple myeloma each year [35].

(a) Mechanism:

The amount of TCDD absorbed by the body depends majorly on 3 factors; the lipophilicity of TCDD, the rate of its metabolism, and the rate at which it binds to the CYP1A2 protein (responsible for metabolism of various chemicals) in the liver. The rate of TCDD metabolism is linked with the presence of Ahr or Aryl hydrocarbon receptor [36, 37], a protein that controls drug metabolism. Ahr is not evolved to the extent to be able to distinguish toxic drugs from non-toxic ones. Thus, it enhances the transcription of a set of genes that produce drug-metabolizing proteins, such as cytochrome P4501A1, 1A2, 1B1 and glutathione S-transferase, which further metabolize TCDD and promote its accumulation in the cells.

3.3.3 Glyphosate:

Glyphosate is an herbicide found in the popular weed killer called “Roundup”. Over the years, many controversial theories have been put forward stating that the chemical was associated with Multiple Myeloma [38]. But a study published in 2020 [39] performed rigorous meta-analysis on various published articles on this topic, and put forward that Glyphosate and Multiple Myeloma do not have substantial correlation. In fact, when the meta-relative risk, or the risk ratio was calculated for MM, with a confidence interval of 95%, the result was 1.03, which proved that Glyphosate did not significantly increase the chances of developing Multiple Myeloma.

3.4 Relation with physical activity

The relation between Multiple Myeloma and physical activity can primarily be understood by linking the former with BMI or Body Mass Index. In this paper, using data obtained from a research article published in 2013 [40], the data was filtered to include ages 50 years and 35 years, and BMI values ranging from <18.5 to 34.9. BMI ranges >35 provided in the paper were excluded. Age range less than 35 years was not included due to lack of adequate data points. The average of the BMI ranges and the number of Multiple Myeloma cases recorded within each range (men and women combined) were taken, and a concise bar plot was generated using R software.

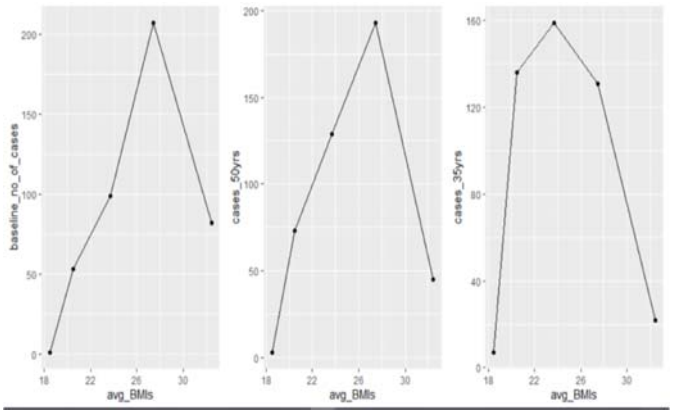

Fig 6: *Relation of Number of MM cases with average BMI. Reference data – [40]*

From the above plots, it can be clearly observed that regardless of age, a BMI ranging between 26-30 (overweight categories) has the highest number of Multiple Myeloma cases. The steady decline of the curves for all 3 graphs can be explained by the fact that the sample population for BMI ranges greater than 26-30, was very less. Hence it can be concluded that obesity contributes to Multiple Myeloma [41]. With respect to physical activity such as exercise, reduced physical activity is inversely related to BMI [42]. Hence lack of adequate physical activity can be pinned down as one of the major risk factors for developing Multiple Myeloma. It is noteworthy to mention here, that this relation is primarily applicable for adults (>18 years), and not for children, as the ability to gain or lose weight is rather flexible during the younger ages.

3.4.1 Mechanism:

Obesity is linked with chronic nutrient overload, which results in excessive production of energy in the body [43]. This energy enhances the over-production of ROS (Reactive Oxygen Species) particles. A variety of obesity-induced factors affect ROS production, such as excessive uptake of glucose and fatty acids, accumulation of T-cells and macrophages in the adipose tissue, and exposure of free fatty acids to smooth muscle cells. Excessive ROS production causes chronic

inflammation which in turn causes DNA lesions which can further result in DNA mutations during the replication process [44]. Although this theory is applicable to obesity's relation with all cancers, the DNA mutated in the plasma cells specifically, causes Multiple Myeloma.

3.5 Relation with Blood Group

Research conducted by an institute in Turkey [45] analyzed the blood groups of 198 Myeloma patients, of which 92 were women and 106 were men, with a median age of 63 years. The blood groups were distributed as follows:

- Blood group A - 46.5%
- Blood group O - 24.7%
- Blood group B - 19.2%
- Blood group AB - 9.6%

A control group of 23,558 cancer-free patients visiting the same hospital, were included and segregated based on blood group. The likelihood of developing MM was estimated for each blood group and it was found that people with Blood Group O, had the least probability of developing Multiple Myeloma. A surprising fact following up is that, those type O patients who did develop MM, had the least chances of survival, given by an increased Lactate Dehydrogenase Level (LDH), a prognostic marker for MM. The mechanism behind this result is yet to be analyzed.

4. Recent Trends in Treatment

Although potential treatment methodologies have been proposed and practiced since 1962, this article is restricted only to recent advancements in the treatment of Multiple Myeloma.

4.1 Diagnosis

Previously, diagnosis for MM used to primarily involve waiting for end-organ failure to show up, after which treatment would commence. Patients were checked for one of the "CRAB" features: Calcium level, Renal failure, Anemia and Bone lesions. This posed a problem for diagnosis as some MM cases not involving direct changes in these levels (such as smouldering MM, which is considered asymptomatic) would not be diagnosed for MM at all. In fact, this delay in treatment is one of the main reasons that Myeloma patients used to have a slippery chance of survival. The International Myeloma Working Group, IMWG, issued revised criteria for MM diagnosis [46], which uses certain "markers" known as Myeloma Defining Events or MDEs, that includes the following: Examination of >=60% clonal plasma cells in the bone marrow; A ratio of involved to uninvolved free light chains, >100, given the absolute level of involved free chains is at least 100mg/L; More than one focal lesion that is >5 millimeters in size. A major advantage of these MDEs is that, either 1 of the 3 given criteria are sufficient for diagnosis of MM, regardless of whether the CRAB features have been detected. Moreover, each criterion individually has been associated with a whopping 80% risk of developing Multiple Myeloma, which only proves the accuracy of the criteria [47].

4.2 Pharmaceutical aspects

The most fundamental struggle that had been faced by scientists for the treatment of Multiple Myeloma was the inability to produce drugs that directly targeted plasma cells. The following drugs have been extensively used for MM treatment, individually and as combinations with other drugs:

4.2.1 *Bortezomib:*

Bortezomib (formula - $C_{19}H_{25}BN_4O_4$), is a proteasome inhibitor that is injected intravenously into MM patients, as a first line of treatment. It is commonly sold under the brand name "Velcade", and was made in 1995 by Myogenics.

(a) Mechanism:

Bortezomib inhibits the activity of the 26s proteasome [48], which is responsible for degrading proteins marked for ubiquitination, in mammalian cells. The drug targets one of the 3 active sites of the proteasome, primarily the PSMB5 unit. The function of the 26s proteasome makes it an extremely important asset for the cell [49, 50]. Thus, its inhibition causes cytotoxicity, ultimately causing the cell to die, either through apoptosis, or necrosis [51]. It has been observed that MM cells are far more dependent on the 26s proteasome than normal cells [52]. The reason for this was explained such that the proteasome's workload is far higher in the former. A post translational modification was observed in various protein subunits of the 26s proteasome, that made it more efficient in the Myeloma cells, and treatment with Bortezomib directly targeted this modification that resulted in reduced proteasome activity. Hence its inhibition is said to cause more harm to Myeloma cells, than to normal cells, which are more tolerant towards the drug. The effect of low-dose Bortezomib on bone formation in smouldering MM patients was reviewed here [53]. On the dark side, Bortezomib is also known to cause certain side effects and toxicity in MM patients [54], which may be caused due to mutations that may occur in the active sites of the 26s proteasome. This leads to resistance of the

Myeloma cells against the drug. For this reason, a secondary drug called Carfilzomib [55, 56] is under trials for treating those MM patient's resistant to Bortezomib.

4.2.2 Elotuzumab and Daratumumab:

In addition to the above mentioned drugs, the FDA in the year 2015, approved 2 monoclonal antibodies, namely Elotuzumab [57] and Daratumumab [58] to treat Relapsed and Refractory MM, also known as RRMM. This improved the survival rates of MM patients [59], although relapses were observed in a few cases, hinting at their limited efficacy [60].

(a) Mechanism:

When administered intravenously, Daratumumab targets CD38 [61], which is heavily expressed by malignant plasma cells or Myeloma cells, compared to normal cells. This ultimately makes the cells undergo either apoptosis or die of cell-mediated cytotoxicity. The Fc component of Daratumumab is a region of importance in the antibody [62], as it binds with Te cells (effector T cells) which allow the effector cells to release toxic substances that increase the toxicity levels in Myeloma cells and finally leads to its lysis. The IgG1 antibody also activates Tc cells (cytotoxic T cells), as an immunomodulatory response. Hence it can be concluded that Daratumumab may contribute towards Myeloma cell destruction through various pathways.

4.3 Combination Therapies

Several combination therapies involving Velcade (Bortezomib) are used to enhance the pharmacodynamics of the drug. The results of such combinations were compiled from several research papers: (i) Velcade plus dexamethasone as an initial therapy regimen for those MM patients eligible to undergo high-dose chemotherapy [63]; (ii) Velcade plus Revlimid plus dexamethasone, also known as VRD therapy, as a treatment for newly diagnosed MM patients [64], and also those who have had a relapse; (iii) Velcade plus Cytoxan plus dexamethasone, also known as VCD therapy, for those patients eligible for a transplant; (iv) Velcade alone, for patients who have already undergone Stem Cell therapy, to extend survival rate; (v) Velcade plus Farydak plus dexamethasone, for patients who have already undergone 2 or more other treatments; (vi) Velcade plus Daratumumab plus dexamethasone, also known as D-Vd therapy, exclusively for patients with RRMM disease [65]. Clinical studies showed that the PFS or Problem Free Survival at 18 months of treatment was increased by 48% from 7% when Daratumumab was combined to this therapy. The Overall Response Rate or ORR to this disease was also significantly increased; (vii) Daratumumab plus Lenalidomide plus dexamethasone, also known as D-Rd therapy, for RRMM patients [66]. PFS at 24 months of treatment was found to be 68% with Daratumumab, and a much lesser 40% without the same. ORR with Daratumumab was significantly raised to 92.9% from 76.4% without the same. An increased PFS rate was also observed for senior citizens falling under the age category of 64 to 75 years; (viii) Daratumumab plus Pomalidomide plus dexamethasone, for patients in whom MM progresses or relapses despite treatment with Velcade and/or lenalidomide. PFS after 1 year for relapse with lenalidomide was found to be 83.2%, while for those with refractory MM with lenalidomide, was recorded to be 72.4%, both of which are significant milestones; (ix) Daratumumab plus Carfilzomib plus dexamethasone, also known as D-Kd therapy [67], for RRMM patients and also for those in whom refractory MM occurred during lenalidomide administration. PFS at 12 months was found to hike at 74%, along with an overall survival rate of 82%; (x) Daratumumab plus Bortezomib plus cyclophosphamide plus dexamethasone, also known as D-VCd therapy, for RRMM patients and also for those patients who have been newly diagnosed with MM (also called NDMM). The 12 month PFS was found to be 66% along with an overall survival rate of 54.5%. These observations were recorded from Phase 2 trials. Further clinical trials are yet to be made. Several other alternative combination therapies are undergoing clinical trials currently [68, 69, 70].

4.4 Entry of nanotechnology as drug therapy

Folate Receptors, or FRs, are surface proteins expressed by every cell in the body, which facilitate the entry of folate into the cell. Folate is essential for maintaining DNA synthesis in the cell [71]. Cancer cells, have mutated genes that overexpress the quantity of FRs on the cell surface, almost by a figure of 500 times the usual quantity in normal cells, thus leading to increased folate uptake, that drives DNA synthesis faster and this ultimately leads to uncontrolled cell division. This concept is applicable to all cancers, although some cancers express more FRs than some others. Therefore, therapies for treating carcinomas focus on targeting the FRs on the cell surfaces, and inhibiting their functions in order to slow down the rate of cancer progression.

The use of nanotechnology to treat carcinomas [72] is rising to fame due to one major limitation of traditional therapies that the former overcomes; the ability to tactfully and precisely target the malignant cells, thus proving harmless to normal healthy cells. The following paragraph talks about a proposal [73] made to use a silica nanodevice made of Mesoporous silica

nanoparticles (also called MSNs) that is loaded with the well-known anti-MM drug Bortezomib, along with Folate as a receptor to the FRs to facilitate the entry of this complex into the cell. These studies were conducted in vitro, where two cell lines were taken, one affected by MM, thus expressing FRs, and another healthy cell line not expressing FRs, and both were individually treated with the FOL-MSN-BTZ complex.

4.4.1 Mechanism:

Silica nanoparticles (the mesoporous ones) are considered the safest to use in the large range of nanoparticles proposed to use for therapy, as they are believed to break down into smaller subunits and finally become water soluble, which are later excreted though urine. Once entering into the body, the MSNs part of the FOL-MSN-BTZ complex quickly identify cancerous cells which express high levels of Folate Receptors. The folate attached to the complex is recognized by the FRs which allow entry of the complex into the cell. Once inside the cell, the components of the complex perform various functions, together as well as individually. As already described, FOL-MSN acts as a vehicle to allow Bortezomib to do its job within the cell; inhibit the 26S proteasome and thus allow accumulation of ubiquitinated proteins to accumulate in the endoplasmic reticulum; thus blocking respiratory pathways and promoting cytotoxicity, and finally activating apoptotic pathways to kill the cell. Now the MSNs also individually play a role in blocking mitochondrial respiration, which prevents production of ATP, thus draining the cell off of its energy. With this, the FOL-MSN-BTZ complex concludes its function within the body. Only a brief description of this therapy has been given here. For more details, the link to the parent article has been provided in [73, 74].

4.5 Autologous Stem cell therapy

Commonly known as ASCT, Autologous Stem Cell Therapy is considered as the standard procedure undertaken for newly diagnosed MM patients after chemotherapy is performed [75]. Although this procedure is not limited to any defined age groups, certain necessary precautions will have to be considered before the treatment is administered to patients above the age of 65 years. Usually a drug called Mozobil is administered to patients before the transplant is initiated. This enhances the number of HSCs being produced by the bone marrow. The procedure of the treatment comprises obtaining hematopoietic stem cells, or HSCs, of a cancer patient, and infusing it back into the same patient to replace the malignant plasma cells in the bone marrow. The significance of this procedure lies in the fact that no issues relating to incompatibility of blood from donor to recipient arise, as the donor is the recipient himself. An important criterion that is taken into account is that, in order to perform ASCT, the cancer patient must be able to produce healthy HSCs [76]. The procedure may be classified into 2 types; called autologous peripheral blood stem cell transplant [77], and autologous bone marrow transplant. The former involves apheresis, wherein a needle is inserted into the vein from one arm, and blood is drawn. The HSCs from the blood are then extracted and filtered, and later pumped back into the body through a different vein [78]. The latter involves obtaining HSCs from the bone marrow, filtering out the healthy cells and injecting them back into the bone marrow. The latter is usually a more preferred procedure as it contains more number of HSCs than blood does.

4.5.1 Criteria to check before ASCT treatment:

- Examination of bone marrow function;
- Blood tests;
- Chest X-ray;
- Surgical history;

Concrete decision on which type of transplant needs to be performed is based on the patient requirements. Just as any other procedure, the ASCT treatment comes with a few side effects, such as nausea, fluctuations in blood pressure, fevers, body fatigue and a change in the patient's taste buds, all of which can be managed with the right prescription of drugs.

4.5.2 Post ASCT treatment:

The post ASCT treatment is an important practice of maintaining the results of the ASCT treatment in the body [79]. A few drugs have been proposed for administration in patients who have undergone ASCT treatment:

(a) Treatment with Thalidomide:

According to a study published in 2014, administration of Thalidomide resulted in a PFS of approximately 10 months, although it did come with a few major chronic side effects, due to which this treatment had to be discontinued. This treatment was further improved by first making the patient undergo High Dose Chemotherapy (HDC) and then ASCT, after which Thalidomide was administered. This significantly improved the PFS values while no significant side effects were recorded, thus proving to be an efficient treatment.

(b) Treatment with Lenalidomide:

Administration of Lenalidomide was done after the patient was made to undergo HDC and ASCT. This resulted in an increase in PFS of 41 months. Although this result made this treatment highly optimistic, concerns regarding Second Primary Malignancies, or SPMs, were made, which had a risk percentage of 6.9% at 5 years post treatment. Second Primary Malignancies are second unrelated cancers that develop in patients who have already had cancer before (the primary cancer). They usually pose as a major risk factor after a patient has undergone chemotherapy or radiotherapy.

(c) Treatment with Bortezomib:

According to Nordic Myeloma Study Group trial, Bortezomib administered as 20 doses to patients after ASCT showed a significant PFS improvement of 7 months. Patients administered with Thalidomide were compared with those administered with Bortezomib, and the latter proved to be more significant in improving PFS and Overall Survival rate as well.

5. Covid-19 in relation with Multiple Myeloma

The Sars-CoV-2 virus is well known for pulling the immune system down once it enters the body. Parallelly, Multiple Myeloma is also responsible for causing immunosuppression, as the number of correct and useful antibodies being created within the system is greatly reduced. Hence a MM patient affected by Covid-19 may be a major cause of concern and approach to treatment must be undertaken with great care to ensure that the treatment of one does not worsen the condition of the other. Current newly-diagnosed MM patients are advised to undergo screening for Covid-19 disease before treatment, because it is believed that MM treatment could exacerbate the active Covid-19 infection [84]. In fact, of all the cancers, hematologic ones have been shown to have the least resistance against Covid-19 [82]. Even those MM patients treated with current standardized Covid-19 vaccines responded with only a low spike in antibody production [85, 86]. Despite this, one paper elaborated on successful treatment of Covid-19 in MM patient, using tocilizumab drug [83]. It has been shown in emerging studies that one of the main motivators behind an increased severe outcome of a Covid-19 affected MM patient, is racial background and ethnicity. As already discussed before, race plays an important role in determining the chance of a person being diagnosed with MM [80]. Of all the races, Hispanics/Latinos and African American Blacks are believed to be the most vulnerable ones, posing a greater risk of mortality in a Covid-19 affected MM situation. A plausible reason proposed for this is the socio-economic background of the races concerned. Apart from this, the usual parameters of MM such as age and gender play an important role is assessing a MM patient's response against the Sars-CoV-2 virus [81]. It is believed that Covid-19 affected MM patients have a high risk of developing thromboembolism or cerebrovascular diseases. Although various studies connecting Covid-19 and Multiple Myeloma are currently ongoing, very little can be explained at this stage about the exact effect that the virus brings about in MM patients.

6. Conclusions

Although rendered an incurable hematological disease, the improvements made in the treatment procedures and diagnosis have reached leaps and bounds over the last twenty years. Survival rates for MM patients have been increased enough for them to be able to lead a healthy life. Various combination therapies aiming at giving patients enough time to survive problem-free are already being practiced. On another perspective, certain precautions can be undertaken by those who have families with a cancer gene, to ensure it doesn't pass on, such as giving the body the right amount of exercise, limiting the exposure to carcinogens, and so on. From age 45 years onwards, frequent diagnostic tests might have to be undertaken to check for any abnormal level of protein build-up in body fluids such as urine, signifying the development of MM or SMM. With the Sars-Cov-2 virus doing its rounds now, MM patients will have to take greater care in ensuring that their comorbidities do not lead to Covid-19 related complications. With the right treatment and care from medical practitioners, the immune system may be strengthened to fight against both the cancer and the virus.

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