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Bone Marrow Cancer caused by JAK2 mutations and related treatments

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Abstract. JAK2 V617F, one of the protein mutations, will cause uncontrolled blood production. The mutation leads to a lot of blood and bone marrow diseases, for instance, myeloproliferative neoplasms, myelofibrosis, leukemia et al. Most of these diseases are deadly. Uncontrolled blood cell production might result in leukemia, myelofibrosis, and bone marrow cancer even worse. However, The development of treatments has not been perfected, so mutations in the JAK2 protein still put patients at risk. This article analyzes the mutation principle of JAK2. Many diseases are caused by mutations. At the same time, experiments have confirmed that JAK2 mutations cross-species and do not only occur in humans. In addition, this article explains the treatment options for diseases caused by JAK2 mutations, such as eBM Treatment and Target Therapy. The research provides the stage that concluded the mutant mechanism and the several treatments for the disease caused by the mutation. Although some of the treatments and therapies are not consummated, the future research orientation could be more focused on the clinical study of target therapies like Parental Proteasome Inhibitors.

Keywords: JAK2 Mutation, Therapies, Bone Marrow Cancer.

1. Introduction

With the continuous improvement of medical technology, some deadly diseases are extremely close to being curable. Nevertheless, one of the things that keeps annoying many medical experts which that cancer research has made a qualitative leap since the 1990s, but existing technologies still cannot cure cancer with a high probability. Except the radiotherapy and chemotherapy, conservative treatment can only prolong the patient's life, but the formers (radiotherapy and chemotherapy) require the patient to bear immense suffering and risk during the treatment process. There were countless types of cancer discovered gradually. The most fatal of these cancers are located on the liver and pancreas, followed closely by cancer of the bone marrow, they can cause various bone marrow disorders. These are known as myeloproliferative neoplasms [1]. The MPNs indicates several reason for causing the tumor primary myelofibrosis, essential thrombocythemia polycythemia vera so on.

Generally, the human body could be treated like a machine, each part is responsible for its own job. When blood vessels are in normal circulation, blood is pumped out of the heart, circulates through the body and back to the heart. It seems like a program that loops through the “machine” day. Sometimes the “components” will emerge “fossilized”. At this point, plenty of diseases or fatal cancers appear, most of which are related to blood diseases such as high and low blood pressure etc. These diseases are more common among the elderly and obese patients. However, when the red blood cells are produced without

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limitations, that will be a huge problem. When blood cells continue to increase and reach a certain critical point, there will be a risk of bone marrow cancer. In fact, Bone Marrow Cancer will not increase endlessly without any reason. There must be some reason to open the "valve" of hematopoiesis. The mutation initiated plenty of disorders and diseases, the researchers and scientists could not afford to wait, so they were looking for countermeasures and treatments. Therefore, the article demonstrates several treatments, they are vary depending on the specific type and stage of cancer, such as Chemotherapy, Radiation Therapy, Bone Marrow Transplantation and Target Therapies [2].

In the past few decades, Bone and bone marrow diseases caused by genetic mutations have emerged endlessly, the most well-known ones being bone marrow cancer and leukemia. Typically, these diseases carry extremely high mortality rates and are difficult to treat. In just a few decades, rare bone marrow cancer has claimed thousands of lives. He did not have lung cancer. Liver cancer is relatively common, so there are very few cases that can be studied. The extremely high mortality rate makes bone marrow cancer one of the most deadly cancers after pancreatic cancer etc. bone marrow transplantation is usually the basic treatment plan for leukemia. However, the painful process of radiotherapy and chemotherapy makes it difficult for already weak patients to survive this stage. At the same time, high medical expenses and extremely long treatment periods make many families unable to afford it. These rare diseases are not covered by medical insurance in most countries. Therefore, some well-off families may have made money for decades, only to be shattered by a disease. With the rapid improvement of medical standards, scientists and researchers are working hard on drug treatment and targeted therapy to achieve the effect of conservative treatment by regularly controlling the secretion of platelets, white blood cells and red blood cells. Although these conservative treatments still require patients to bear high medical expenses, some lower-cost drugs have been allowed to be included in medical insurance, and the state bears the cost of drug development. In the early stages, these targeted treatments and medications can be of great help to patients. Nevertheless, under some conditions, “depending on the type of cancer, no treatment other than observation may be indicated. In this instance, it is called watchful waiting [3].

2. Mechanism, Experiment and Treatments

2.1. Mechanism

Based on two weeks of research on how bone marrow cancer is present in the human body. This paper found that there was a significant gene called Janus kinase 2 (JAK2). Initially, the function of the JAK2 gene is stimulating cell growth and division, yet, one of the amino acids named Valine was substituted by another amino acid called Phenylalanine. This is referred to as JAK2 V617F Mutation. One of the articles explains the replacement appeared which proves this causes the JAK2 protein to be constantly switched "on," leading to uncontrolled blood cell production [4]. Uncontrolled blood cell production highly improves the probability of Myeloproliferative disorders, Polycythemia Vera, and Primary Myelofibrosis. Myeloproliferative disorders are the most representative disease, and generally, the early stage will lead to thromboembolism, rupture of blood vessels, and subcutaneous hemorrhage. Most of these situations are controlled, but when the patients delay the treatment cycle or even ignore these circumstances; meanwhile, leukemia and myelofibrosis will occur. At this stage, being cured is almost impossible to complete, and usually, in this case, only radiotherapy and chemotherapy can be used to delay the patient's survival cycle.

2.2. Experiments

One of the noted experiments illustrates that JAK2 V617 Mutation is also happening across species, but also certify the mutation mechanism. The researchers “insert” knock-in transgenic mice which obtained JAK2V617F(mutation) called “PF4iCre” mice. The JAK2V617F/WT mice were generated by crossing JAK2V617F KI mice with PF4iCre transgenic mice. After 25 weeks of observation, the results have been confirmed between these two different gene mice. According to the five disparate types of control groups from the experiment, the results are obviously shown.

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They respectively are HT which stands for Essential Thrombocythaemia; platelets, leukocytes and granulocytes. These are like the foundation of a building, forming a system. To give a simple example, platelets are well known, and when human skin is injured, platelets will continue to appear until the wound is healed. At the beginning of the first 8 weeks. These four types of blood cells do not show a significant difference when compared to JAK2WT mice and JAK2 V617F mice. In contrast, since the initiation of 10 weeks, the gap is getting bigger between the comparison. Platelets and white blood cells, in particular, showed significant growth in the V617F mutant mice. At 25 weeks, platelets even reached a difference of 2500 (G/L). When taking a look of the second set of data, the comparison is straightforward enough to emphasize the difference between the size of the spleen, which is also termed "splenomegaly". The term splenomegaly indicates spleen enlargement. Through observation, it can be clearly seen that the diameter of the spleen of V617/WT mice is almost double that of the former. This can also prove that excessive secretion of blood cells leads to organ enlargement due to overload. Meanwhile, the fibrosis of tissue occurs during the amount of leukocytes raised. Myelofibrosis is a typical representative of the uncontrolled production of leukocytes. Myelofibrosis occurs in a variety of malignant and non-malignant disease states. The deposition of reticulin and collagen fibers in the bone marrow of patients with myelofibrosis is thought to be mediated by myelofibrotic hematopoietic stem/progenitor cells, thereby contributing to the effects of myelofibrosis. The damaged microenvironment is conducive to malignant hematopoiesis and not conducive to normal hematopoiesis. Therefore, myelofibrosis is also one of the early stages of bone marrow cancer. It has been reported that the expression of JAK2V617F in all myeloid lineages demonstrates the clonal origin of this MPN phenotype [5].

Generally, the experiment prudently constructs the control group between transgenic mice with JAK2 V617F Mutation and another does not appear the mutation. All V617F mutations have a high probability of causing uncontrolled production of blood cells. Excessive production of platelets can cause vital organs such as the spleen to enlarge and become overloaded. In addition, the secretion of large amounts of white blood cells will accelerate bone marrow proliferation and lead to myelofibrosis.

Fortunately, research shows that JAK2 V617F is not inherited from parents. The mutation is acquired, which indicates it must happen from the influence of external factors, like long time being exposure to radiation, smoking or alcoholism. According to a patient's description, he has been approved for twice the mutation of V617F. From now on, he does not receive any negative feedback like pain or discomfort. He merely got in positive for V617F mutation. In contrast, the doctor strongly recommended that he maintain the balance of blood cells in the body through appropriate bloodletting. Although the body did not suffer huge damage in the early stages of mutation, treatment cannot be ignored.

2.3. eBM treatment

There are tons of treatments that could be used for Bone Marrow Disease. One of the well-known treatments is called "Engineered Bone Marrow" (eBM). It dedicates the potential treatment for osteosarcoma. When using eBM to treat osteosarcoma, it is quite likely that a successful course of treatment can be identified through biopsying and culturing each particular tumor prior to starting therapy. In one study, mice were implanted with thinned osteogenic material to create eBM, and eight weeks later, the material was examined utilizing cellular constructs. This study compares mouse and human samples to investigate the effect of anatomical implantation sites on eBM tissue quality. Through investigation, this study discovered that eBM can manufacture relevant components of genuine bone marrow in a stable manner. To attain optimal treatment standards, simulation experiments in intricate bone marrow cell structures can be carried out based on the eBM mechanism and function. In addition, eBM can also be used to screen drug treatments for diseases [6].

2.4. Target therapy

Targeted drug therapy is a drug therapy that is administered in a specific way. Patients are treated regularly (in combination with drugs) to target specific controlled therapies that find cancer cells in the human body. The specific working mechanism containing the target therapy may include enzymes,

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proteins or gene mutations that may be driving the cancer's growth [7]. This is an adjunct treatment, usually accompanied by other treatments, such as chemotherapy, and radiation. In this way, the benefit of targeting cancer cells is maximized. The pathology tests include the examination of tissue samples, blood samples or matrix samples. When looking for mutated or excess proteins in cancer cells, pathologists can identify potential therapeutic targets. They may also find abnormalities in the cells within the cancer cells. These abnormalities usually be indicated by the mutant protein, just like JAK2 mutations, also known as V617F. The progress of target therapy has been described that [8] "In the beginning, the medical target turns off signals that allow tumors to grow, then prevents cancer cells from producing new blood vessels to provide nutrients to tumors. Stopping the production of growth that may contribute to tumor growth. The target repairs the ability of cells to shut down when defective. Finally, delivers radiation or chemotherapy drugs directly to mutated cells".

2.5. Long-term Parental Proteasome Inhibitor

There is another treatment that corresponds directly with multiple myeloma names "Long-term parental proteasome inhibitor (PI)". It belongs to the target therapy. For patients diagnosed with Multiple Myeloma who are not candidates for bone marrow transplantation, PI therapy is the underlying option. Adding PI to both drug regimens significantly improved overall survival. On the contrary, during the adjuvant treatment of PI, it will produce certain toxicity. Based on the patient's comprehensive complications, dangerous physical conditions, and long and repeated treatment caused by the burden. Therefore, at this stage, PI cannot have a significant clinical effect in a large and efficient manner. In addition, PI therapy also has relatively harsh requirements for the age of the patient. Studies have shown that when strict trial standards are implemented, because the patients participating in randomized controlled trials are young, healthy, energetic, etc., it will lead to the result that the subjects are more resistant to drug effects [9]. Therefore, During the trial, the treatment process of the test subjects should also be marked. Some studies have used this kind of marking. Data from this study suggest that, in addition, newly diagnosed multiple myeloma patients who are not eligible for transplantation or who have had a transplant delay of ≥2 years are eligible for transplantation, and these patients are also considered potential targets [8]. The treatment cycles and methods for these patients are as follows: After three cycles of bortezomib-based induction therapy, the results of patients who took Ird has been shown in table 1.

Table 1. Three cycles of Bortezomib-based induction therapy [8].

Dose	Medical Type	Days
4mg	Isazomib	1, 8 and 25
25mg	Lenalidomide	1-21
20-40mg	Dexamethasone	1, 8, 15, 22 and 28

140 patients chose to participate in the therapy program. Calculated baseline creatine clearance values among all patients are presented beneath in table 2.

Table 2. Calculated baseline creatine clearance values among all patients [8].

Baseline Creatine Clearance Values	Patients Amount	Percentage of All
<60 mL/min	40 patients	28.6%
≥60 mL/min	96 patients	68.6%
Missing Data	4 patients	2.9%
Had ≥1 concurrent medical condition	131 patients	93.6%
Had peripheral neuropathy	18 patients	12.9%

The study treated patients with common treatments: one was bortezomib-lenalidomide-dexamethasone, used in 118 patients; the other was bortezomib-cyclophosphamide-dexamethasone, Used in 18 patients. Three of the patients completed 26 treatment cycles according to the original study

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protocol and received autologous stem cell transplantation after IRd. The three patients in this study who were cured by PI therapy had their bone marrow cancer growth suppressed. This suggests that proteasome inhibitors block the action of the proteasome, which finds the cancer stem cells and then breaks down the mutated protein [10].

3. Conclusion

In general speaking, the mechanism of JAK2 V617F Mutation is the amino acid "V" which stands for Valine which replaced by the amino acid "F"—Phenylalanine. When the replacement occurs, the "switch" turns on that blood cell is producing uncontrollably. At the early stage of mutation, People's bodies will not be affected too much, but compared to ordinary people, the values of important blood cells such as PVs platelets and white blood cells will be significantly increased. In the middle stage, health-threatening diseases such as Myeloproliferative neoplasms and Polycythemia vera gradually develop. At this stage, the burden on certain organs of the body, such as the spleen and heart, will increase. In the final stage, when the number of white blood cells reaches a critical point, there is a risk of leukemia. In addition, PV will continue to develop into myelofibrosis and also increase the probability of bone marrow cancer. Besides, through the experiment, The researchers found out that JAK2 Mutations could also occur across species. The researchers hold knock-in transgenic mice with V617F mutation and another mouse generated from these mice. In this study, all data point to mice with the direct V617F mutation having significantly higher blood cell counts than control mice. For example, the number of platelets and white blood cells far exceeds that of indirect mice at 25 weeks. Another example is the size and weight of the spleen. The former is almost twice that of the latter. It is enough to see that the V617F mutation causes a great burden on the body, and if left unchecked for a long time, it can lead to the occurrence of leukemia or bone marrow cancer. Overall, mutations of the JAK2 gene cause numerous blood and bone marrow diseases. These diseases can be diversified, such as myelofibrosis, leukemia, and bone marrow cancer. The probability of their cure is very limited. Usually, long-term chemotherapy and radiotherapy can prolong the patient's life but it is limited. Although the treatment rate is low and there are few treatment options, the research and development of the eMB treatment plan and Inhibitor Therapy which are introduced in the article are also actively carried out. Most of the treatment options covered in this article are true for individual cases, but the downside is that they do not take into account a broad age range of patients. For example, Inhibitor Therapy targets younger patients because older patients often cannot tolerate the negative effects of heavy medication. Therefore, in future studies, it is recommended to focus more on the applicability of inhibitor therapy in the elderly population.

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