The treatment of cancer cell therapy: Monoclonal antibodies and Vitrakvi

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Abstract: Cancer is a disease that confuse and torment people for hundreds of years, while human only know a little about it and the treatment seems not as effective as expectation. For many of years, scientists were seeking new treatments, the latest one was called targeted cancer cell therapy. Ideally, it targets on cancer cells and kill them without harming the normal cells, which is totally different from chemotherapy. Targeted cell therapy mainly based on medicines that can promote body immunity or weaken the cancer cell. There are several kinds of drugs that are commonly used in targeted cancer cell therapy, monoclonal antibody, agiogenesis inhibitors, proteasome inhibitors and signal transduction inhibitors.[1] For example, some monoclonal antibodies can help white blood cells to identify cancer cells quicker, while the others can help to destroy cancer cells from inside like a poison. [2] For every different kind of cancer, which means the different location of tumor, different kind of drug is used and their effectiveness is different. In this easy, two kinds of targeted cancer cell therapy used drugs will be discussed and evaluated.

1. Introduction

Cancer has been existing for thousands of years, it isn't caused by bacteria or virus, it is the defect of human caused by the mistake of cell replication. When cells are replicating their DNA code and divide into two cells, the mutation takes place in oncogene and causing a mutating cell which usually has super reproductive ability. When a large number of mistaken cells gather, it grows into a tumor and when tumor metastasis happens, this is cancer. In modern society, the treatment of cancer is mainly divided into two ways, targeting and chemotherapy. Targeted cancer cell therapy can save normal cells and kill cancer cells but it isn't working all the time, for some specific cancer the targeting drug does not work which is the reason that more people prefer chemotherapy. Chemotherapy is very well-known, this drug kills all the cell which will make human body weak but most time it is effective. Moreover, it is also effective when shrinking the tumor in order to do a surgery. [3]

For most of the drugs used in cancer therapy, nanomedicines take a lot of percentage. Nanomedicines contribute to increase the white blood cells and concentration of drugs around the cancer or tumor tissues, promoting patient's immunity and weakening the cancer cells. [4] Moreover, nanoparticles can be bio-engineered to bind to some specific molecules or atoms which can help to deliver drugs to their targeted cells.[5]

Monoclonal antibody (mAbs) is a wide range of antibodies referring to the copies of antibody we have in our body, several of them are used in cancer targeted treatment. Antibodies work by themselves without the help of drus or radioactive material. Most of them work by attaching to antigens on cancer cells and marking it for immune system.[6]

Vitrakvi is the drug invented specifically to treat the tumor that has a mutation on "NTRK" genes, it can stop the growth of cancer cells by blocking the TRK protein which is responsible for the cell growth.[7]

In this review, we will give out two specific drugs, monoclonal antibodies and Vitrakvi, which are usually used in targeted cell therapy of cancer, including the basic structure and working principles of them; as well as the impact and side effects of those drugs on human body based on recent science reasearch and data. By identifying the effectiveness, we will give an overall evaluation.

2. Monoclonal antibodies

Monoclonal antibodies are the copies of normal antibodies in human bodies but it is used in labs for experiment. “Antibodies” were first defined as ‘neutralizing substances found in blood’ by Doctor Behring and Doctor Shibasaburo in 1890.[8] After almost a century, it was re-identified as proteins that can bind to antigens by Doctor Heidelberger and Avery. Until 1947, it was found that antibodies were produced by plasma B cells and it was specific to different anitgens.[9]

Antibodies are made by long chain of glycoproteins which belong to immunoglobulin (Ig), a huge family. Their role in human body is to identify antigens and bind to them which helps white blood cells to eliminate the invaders. For a normal antibody, it has two heavy chains inside, side by side forming a ‘Y’ shape, and two light chains beside each heavy chain, the tips of light chain and heavy chain form antigen binding site. In the space of the middle of ‘Y’ shape, the variable region, usually composed of 110~130 amino acids, which gives the antibody a specificity for binding different antigens. The antigen binding site can be controlled by bio-engineering the amino acids that form the chains so that antibodies can bind to specific cancer cells.[10] Monoclonal antibodies are slightly different, they are made of murine, chimeric, humanized which are made form mouse proteins, and human proteins.[11]

Antibodies exist as 5 different forms in which the different variable regions and give them different functions. They are IgA, IgD, IgE, IgM, IgG, while IgG is most commonly used in cancer treatment.[12] There are two antigen binding fragments (Fabs) and one constant fragment (Fc). The Fabs determined the specificity of the antibody in terms of complementary th determine regions (CDRs), while Fc help the antibody to connect with immune system by involving Fcγ receptors (FcγRs) on natural killer cells (NK), and it is also thought to protect antibodies in blood from degradation.[13]

Targeted monoclonal antibodies have variety of ways to cause cancer cells to death. On of the most important mechanisms is to block the growth protein and signaling receptor which are usually overexpressed in cancer cells, or inhibit the ability of specific soluble mediators to bind to receptors or simply target on the membrane bound receptors, where thay act as agonists and antagonists.[14] For instance, epidermal growth factor receptor (EGFR) in cancer cells causing the invasion, metastasis, proliferation of tumor can be blocked by Cetucimab, while the patients who have mutation in KRAS and BRAF genes can also use it as treatment.[15]

Other types of antibodies like naked antibodies and immunoconjugates are mainly used in immunotherapy of targeting therapy, which is aiming for restoring white blood cells and strengthen immune system of the patient against cancer cells.[16] The role of antibodies here is to mark the cancer cells to make them more noticeable for immune cells or bind to the proteins on the surface of cancer cells to modulate T-cells.[17] Several monoclonal antibodies have been accepted and used in clinical treatment as immunotherapy like rituximab (1997), ibritumomab tiuxetan (2002), trastuzumab emtansine (2013), nivolumab (2014) and pembro lizumab (2014).[18]

In order to further control the anti-tumor features of monoclonal antibodies, several attempts have been made to produce antibody-like molecules that can chemically replace antibodies’ role in our body. Antibody-like molecules can be bispecific which means they can bind to two proteins in cancer cells, they are usually lacking the ability of Fc domains but having two unidentifiable Fab regions. They are also called bispecific antibodies or bispecific tri-functional antibodies (triomabs) if they have functional Fc domains and this contributes to the ability to bind cancer cells and immune cells at the same time maintaining Fc dependent effector functions such as CDC (Complement Dependent Cytotoxicity) and ADCC (Antibody dependent Cell-Mediated Cytotoxicity).[19]

The side effects can never be ignored, a common reaction to antibodies is being allergic to drug used so it is usually taken together with other rejection drugs. Patien might feel nausea, easy to catch a fever, breathless, vomiting, diarrhea, decreasing blood pressure, rashes and headache.[20] There are some specific side effects which can be serious, for example, it might cause heart problems and kidney problems.[21]

3. Vitrakvi

Vitrakvi, also known as larotrectinib, was launched in the United States on December 18, as a targeted drug, Vitrakvi is different from traditional anti-cancer drugs. Vitrakvi does not target tumors located in certain organs or tissues. Its targets are defined based on NTRK genes.[22] As long as you have a tumor caused by the gene or have serious complications due to surgical removal of the cancer, you can use this medicine regardless of the type of tumor. NTRK is a membrane-bound receptor, which plays an important role in the development of the central nervous system. TrkA is highly expressed in cholinergic neurons of the sympathetic nerve, trigeminal nerve, dorsal root ganglion, forebrain and terminal cortex; TrkB is highly expressed in the entire central nervous and peripheral nervous system; and TrkC is mainly expressed in mammals Expressed in nerve center tissues. Trk kinase receptors are also widely distributed in human non-neural tissues. For example, the expression of TrkA or TrkB can be found in organs such as salivary glands, stomach, intestines, pancreas, bone marrow, adrenal glands, prostate, ovaries, uterus, and bone marrow muscles. Regulated by nerve growth factor, it activates the MAPK pathway to help cells differentiate or proliferate. MAPK pathway is a very important part of cancer research. Its overactivation is directly related to cancer, and it is related to the occurrence and development of breast cancer, esophageal cancer, gastric cancer, liver cancer, and colon cancer.[23]

NTRK gene also includes NTRK1, NTRK2 and NTRK3, which are called Neurotrophic Receptor Tyrosine Kinase and belong to receptor tyrosine kinases (RTKs). RTK is very special. It is both a receptor and an enzyme that can phosphorylate tyrosine residues on proteins. [23]

The active drug in Vitrakvi is larotrectinib, which is a kinase inhibitor.larotrectinib can inhibit receptor tyrosine kinases,The receptor kinase gene molecule will undergo mutations, especially the fusion with other genes, which play a role in cancer.[24] Therefore, by inhibiting certain substances in the MAPK pathway, it can inhibit the occurrence of cancer. In essence, Vitrakvi can be regarded as one-third of the MAPK pathway inhibitors, because NTRK is not only related to the MAPK pathway, but also AKT and PLCγ Two pathways related to cancer are also activated by NTRK. By inhibiting the chimeric protein produced by the TRK fusion gene, cancer patients carrying the TRK fusion gene can be treated. Vitrakvi uses this method to inhibit the activity of NTRK chimeric protein, thereby slowing down the proliferation of cancer cells and slowing down the progression of cancer.The effect of TRK fusion on cancer. In malignant tumors, TRK sometimes produces gene fragment rearrangements. For example, in KM12 cells (such as colon cancer), TRK will fuse with TPM3 to form a chimeric gene, which is transcribed into TPM3-TRKA chimera protein. This protein can also regulate the three pathways regulated by NTRK, but is no longer regulated by nerve growth factor, so that the intracellular TRKA is over-expressed and continuously activated, which leads to the over-activation of MAP, AKT and PLCγ, and accelerates the growth of cancer cells. Proliferate and inhibit their apoptosis.[25]

The New England Journal of Medicine has published the results of clinical studies on the efficacy and safety of Vitrakvi. The study shows that from cancer patients aged over 4 months to under 76 years old, the overall effective rate for 17 different types of cancer Probably around 75%. Of all the patients treated, 75% of the tumors shrank by 62% or disappeared by 13%. However, the effective rate of 75% refers to the proportion of patients whose tumor target lesions have shrunk by more than 30% after the use of Vitrakvi, and does not represent the proportion of cured tumors. According to data published by the FDA, 73% of patients have a response time of more than 6 months after using vitrakvi, 63% of patients have a response time of 9 months or more, and 39% of patients have a response time of 12 months or more. But it is only suitable for patients with NTRK gene fusion, and the number of cancer patients with NTRK mutation is very small. [26] At present, Vitrakvi has been approved in many countries and regions around the world, including the United States, Brazil, Canada, and other 40 countries. In Japan, the Vitrakvi NDA submission is based on the combined data of 102 patients in the Phase I trial of adult patients, the Phase II NAVIGATE trial of adult and adolescent patients, and the Phase I/II SCOUT trial of pediatric patients. In these trials, Vitrakvi was investigated and treated more than 20 solid tumors with different histologies, including lung cancer, thyroid cancer, melanoma,

gastrointestinal stromal tumor, colon cancer, cholangiocarcinoma, soft tissue sarcoma, salivary gland cancer and infants Fibrosarcoma and so on.[27] Of the 102 patients, 93 patients were from the main analysis group, and the other 9 were patients with primary central nervous system (CNS) tumors. The results showed that Vitrakvi treatment showed a high remission rate, long-lasting and rapid remission. The specific data are: the main analysis set shows that the overall response rate (ORR) is 72%, of which the complete response rate (CR) is 16%, and the partial response rate (PR) is 55%. In another additional analysis that included patients with primary CNS, ORR was 67%, with CR of 15% and PR of 51%. At the time of the main analysis, the median time to the first remission of patients.[28] receiving Viktarvy treatment was 1.81 months. At the time of analysis, the median duration of remission had not been reached (range: 1.6+ to 38.7+ months), and 75% of patients had remission duration ≥12 months. Of the patients who received treatment, 88% were still alive one year after the start of treatment. At the time of analysis, the median progression-free survival (PFS) had not yet been reached. The safety of 125 patients with NTRK gene fusion was evaluated. Most adverse events (AEs) were grade 1 or 2, and only 3% of patients had to permanently stop treatment due to AEs that occurred during treatment. Nineteen (15%) patients reported dose reductions, of which 10 (8%) were due to adverse events. Most adverse events leading to dose reduction occurred during the first three months of treatment. Viktarvy'streatment of TRK fusion-driven cancers in adults and children has clinically significant improvements in patient quality of life. In two global multicenter clinical trials, 60% of adult patients reported an improvement in their health scores. For pediatric patients, 76% of patients reported an improvement in the PedsQL total score.Applications in other regions are ongoing or planned.And every medicine has side effects, and so does vitrakvi. After starting the medicine, you may feel stomach upset, vomiting, constipation, diarrhea, stomach pain, or back, muscle or joint pain.Although Vitrakvi is effective, the price is unaffordable for most cancer patients. For example, children are mainly based on oral liquid formula, which costs at least 11,000 dollars a month. The larger the disease area, the higher the cost. High; while adults are mainly capsules, the 30-day dosage is about 32,800 dollars. The high price has also aroused the suspicion of patients' families.[30]

At present, Bayer said that patients will not be unable to afford it, and most patients' monthly out-of-pocket expenses will be US$20 or less. Their company will help patients pay expensive fees and will provide Vitrakvi free of charge, while developing insurance details. If the patient cannot afford the drug, a charity funded by Bayer will provide the drug free of charge. Bayer also promises that if the patient does not show clinical results in the first 3 months of treatment, it will refund all expenses of the payer such as the insurance company or individual.[29]

4. Conclusion

At present, there is sufficient evidence to prove the great application value of anti-growth factor receptor monoclonal antibodies for the treatment of human cancer. At the same time, in the current research, these two aspects of research have attracted widespread attention: the disorder of growth factor receptor function caused by monoclonal antibodies and the positioning of molecules and therapeutic agents mediated by monoclonal antibodies. Clinical treatment research in these areas is also being actively carried out. The methods and applications described above are the specific applications of these two aspects, and in future research, there are several other aspects that are worthy of further in-depth, such as the cell cycle disorder of tumor cells in the absence of growth factors. The study of the mechanism of cell death, the enhancement of the efficacy of the combination therapy of monoclonal antibodies and other treatments such as chemotherapy, signal transduction inhibitors, etc. In terms of recombinant antibody molecules, how to design and produce new and more effective antibody-based multifunctional fusion molecules is the most critical problem we have to solve.

The 75% effective rate of vatrkvi only means that the total single-path measurement of the lesion can be significantly reduced after using the drug, and the proportion of patients with a reduction of more than 30% accounts for the proportion of all treated patients, not that it is cured. However, it is undeniable that the standardized use of the drug can indeed make the tumors in some cancer patients

disappear and enable them to achieve long-term survival, which is also one of its main advantages. Vitrakvi does have a very ideal effect on a variety of cancers, but it also has certain limitations. It is not suitable for every cancer patient. It can only be used by cancer patients with NTRK fusion gene, and this oncogene occurs in the tumor. The rate is extremely low, and brain tumors are relatively high, but they are all less than 1.4%. Therefore, before cancer patients use the drug, they need to test for the fusion gene. Only cancer patients who meet this condition can use vitrakvi.

Cancer is very painful. It is hoped by everyone that cancer can be cured as soon as possible. We are still exploring cancer research. The emergence of Vitrakvi gives us more hope. I believe that with medicine There will be better news waiting for us in the future.

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