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Research Progress on Drug Combination Therapy for Multiple Myeloma

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Abstract: Multiple myeloma (MM) is a malignant hematological disease of plasma cells. It's the second most frequent hematological malignancy and is highly heterogeneous and complex. In recent years, the pathogenesis of multiple myeloma has been studied in depth, and new drugs are continuously emerging; the strategy of drug combination therapy of treating multiple myeloma has made great progress. The research progress of drug combination therapy for multiple myeloma is reviewed with emphasis on the combined application of proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, and other drugs, and the clinical effects of the above drug combination regimens in different treatment stages (induction therapy, consolidation therapy, maintenance therapy). The studies have demonstrated that drug combination regimens can significantly enhance the complete remission rate of patients, prolong the progression free survival and the overall survival, improve the quality of life of patients, overcome drug resistance, and achieve the effect of overcoming drug resistance through the combination of drugs with different mechanism. Nevertheless, drug combination has some challenges, like drug interactions and adverse reaction management, and further treatment regimen optimization will be required to achieve precise treatment. The biological characteristics of multiple myeloma are not fully understood, and new drugs are continuously being developed, making the drug combination therapy for multiple myeloma have a broad development prospect that day.

Keywords: Multiple myeloma, Drug combination, Proteasome inhibitors, Immunomodulatory agents, Monoclonal antibodies

1. Introduction

1.1. Research background

MM is a cancer of plasma cells characterized by the production of monoclonal immunoglobulins or light chains, leading to the uncontrolled growth of clonal plasma cells in the bone marrow. This results in clinical manifestations such as bone damage, anemia, hypercalcemia, and kidney dysfunction. Although recent advancements in treatment have enhanced patient survival, MM remains an incurable condition. Conventional wat to treat MM such as approaches, including radiotherapy, hematopoietic stem cell transplantation, and chemotherapy`, often face limitations in effectiveness and can lead to drug resistance. In recent years, a deeper understanding of the disease's pathogenesis has led to the development of novel therapies, such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, which are now being integrated into clinical practice. These drugs work

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through different mechanisms that inhibit tumor cell proliferation, induce apoptosis, and regulate the immune system, & so bring new hope against multiple myeloma. However, single drug monotherapy usually fails to provide a satisfactory therapeutic effect. As a result, drug combination is a hot spot of the current research. Multiple mechanisms can be exploited for drug combinations to exert synergistic effects of increasing efficacy and reversing drug resistance in improving therapeutic outcome, and prolonging patient survival. For instance, the cytotoxic effect on tumor cells can be improved by a combination of proteasome inhibitors and immunomodulatory agents; a combination of monoclonal antibodies and chemotherapeutic drugs can increase drug targeting and reduce toxicities to normal cells. Furthermore, drug combination allows for to development of personalized treatment regimens according to the condition of a particular patient (e.g., age, physical state, and stage of a disease) to enhance the safety of a treatment. Thus, the investigation of drug combinations is of significant clinical importance in multiple myeloma.

1.2. Research significance

Drug combination study is of great importance for multiple myeloma in various aspects. To begin with, a drug combination would greatly enhance our treatment response rate and survival rate of patients from the standpoint of clinical treatment. The efficacy of targeting various aspects of cancer cells is significantly boosted when drugs with different action mechanisms are used in conjunction. For instance, pairing the proteasome inhibitor bortezomib with the immunomodulatory drug thalidomide can dramatically increase the number of complete remissions and extend the period of progression-free survival by 1-2 years[1]. This is of great importance in achieving improved prognosis of patients suffering from multiple myeloma and improved quality of life related to the disease. In addition, a drug combination study overcomes the problem of drug resistance. MM is one such disease for which drug resistance is a major challenge in treatment. Drug resistance quickly develops in tumor cells when single-drug monotherapy is used. Drug combination, however, can itself display dosing effects through several mechanisms that decrease tumor cell dependence on a single agent drug, and that can slow the development of drug resistance. For instance, the immunomodulatory agent lenalidomide combined with dexamethasone can resolve the therapeutic dilemma after bortezomib resistance, giving the patients more treatment alternatives[2]. Likewise, the research on drug combinations can enhance knowledge on the pathogenesis of multiple myeloma itself. The reason for this is that the biological characteristics of tumor cells are different, and the mechanisms of action of different drugs are different. Further study on the effects of drug combination reveals further tumor cells' signaling pathways, cell cycle regulation, and apoptosis mechanisms, which would set up the basis for the development of new therapeutic targets and drugs. The study of drug combinations finally helps to promote the development of an individualized treatment. In multiple myeloma, there are wide differences among patients in the physical condition of the patient, different disease characteristics, and differences in gene expression profiles. Individualized treatment regimens thus need to be formulated. Based on specific conditions of patients, the drug combination will choose appropriate drug combinations and dosages to achieve precise treatment, improve the safety and efficacy of treatment, reduce medical costs, and bring greater therapeutic benefits to patients.

1.3. Literature review

The study of drug combinations for the treatment of MM has progressed a lot in recently. On the other hand, bortezomib and carfilzomib are two common drugs regarding proteasome inhibitors. Bortezomib causes tumor cell proteins to accumulate through inhibition of proteasome activity, finally resulting in apoptosis. The monotherapy with bortezomib yields an overall response rate of

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about 30%-40 %, whereas the combination with thalidomide and dexamethasone increases the overall response rate up to 60%-70 % and almost doubles the complete remission rate[1]. Second-generation proteasome inhibitors include carfilzomib, which is more active and less toxic. It has recently been shown that in patients with relapsed and refractory multiple myeloma, the combination of carfilzomib and dexamethasone attains an overall response rate of 50%-60 % and can be well tolerated. Immuno modulatory agent include thalidomide, lenalidomide, pomalidomide are the commonly used drugs. Besides immunomodulation and anti-angiogenesis, thalidomide has several adverse side effects, which include neurotoxicity and thrombosis. Thalidomide (derivative) has less neurotoxicity but stronger immunomodulatory effects. Lenalidomide combined with dexamethasone can provide effective treatment in combination with newly diagnosed MM in the way of extending median progression-free overall survival to 5-6 years. The immunomodulatory agent pomalidomide still has some therapeutic effect in patients refractory to lenalidomide. The use of daratumumab and isatuximab drugs has been a miracle in the development of monoclonal antibodies in the treatment. Given that daratumumab is a monoclonal antibody that targets CD38 and leads directly to tumor cell apoptosis and indirectly to greater tumoricidal capacity of the tumor cell through immunomodulatory effects, its addition to induction therapy is likely to compensate for suboptimal DLT clearance in this population. Daratumumab plus bortezomib and dexamethasone for the treatment of relapsed and refractory multiple myeloma may obtain an overall response rate of 70-80 %, increase the complete remission significantly, and prolong the median progression-free survival to 18-24 months. Its therapeutic effects are also good when it is combined with pomalidomide and dexamethasone to treat relapsed and refractory multiple myeloma, and it is a monoclonal antibody targeting CS1. However, different progress has been made at different treatment stages in the research of the drug combination regimens. Multiple drug combination regimens (such as [VTD regimen] have been widely used in the induction therapy stage of newly diagnosed patients with an overall response rate of 80% to 90% and a complete remission rate of 30% to 40%[3]. During the consolidation therapy stage, the patient can continue deeper remission with autologous hematopoietic stem cell transplantation together with drug consolidation therapy to prolong survival. With the advent of maintenance therapy with lenalidomide, bortezomib, and other drugs from the maintenance therapy stage can result in a significant extension of the progression-free survival of patients[4]. Furthermore, the good prospects of CAR-T cell therapy and bispecific antibodies are observed in a drug combination study, as well. The response rate and survival of patients with refractory and relapsed multiple myeloma are dramatically increased when CAR-T cell therapy is added to traditional drugs[3]. Bispecific antibodies increase the immune system's killing capacity of tumor cells by combining binding to tumor cells and immune cells. Together, these new drugs offer additional options and hope for better treatment of multiple myeloma. To conclude, extensive efforts have been made in the study of drug combinations for multiple myeloma in recent years. Despite their increased efficacy and improved survival of patients, the treatment regimens combining multiple drugs have yet to reach the target of a precise or individualized treatment. With this future knowledge of the biological characteristics of multiple myeloma and new drugs, a broad development prospect of drug combination therapy for MM may be available.

2. Current status of drug combination therapy for multiple myeloma

2.1. Common drug combination regimens

Hematological malignancy called multiple myeloma (MM) is an extremely heterogeneous disease, and treatment seeks to prolong survival, improve quality of life, and decrease symptoms. With the appearance of new drugs, drug combination regimen has increasingly become an efficient strategy for this disease in recent years.

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One of the key drugs to treat MM is proteasome inhibitors (PIs). The first proteasome inhibitor for the treatment of multiple myeloma is bortezomib. The proteasome is inhibited, and proteins thus accumulate within tumor cells, and apoptosis is induced. Despite this, however, bortezomib has certain limits of use; for example, peripheral neuropathy is an adverse reaction. To overcome the limitations noted above, the second-generation proteasome inhibitor carfilzomib was developed. Carfilzomib carries the mechanism of action of an epoxyketone proteasome inhibitor, and selectively and irreversibly binds both constitutive and immunoproteasomes. The Kd regimen is highly effective in the treatment of relapsed/refractory multiple myeloma (RRMM) in clinical trials. The median PFS of the Kd regimen has doubled compared to the bortezomib and dexamethasone (Vd) regimen. Moreover, carfilzomib has also been investigated in combination with lenalidomide and dexamethasone (KRd) regimen, which leads to a good treatment effect in newly diagnosed multiple myeloma (NDMM) patients.

Another category of drugs for the treatment of multiple myeloma is immunomodulatory agents (IMIDs). Immunomodulatory agents like lenalidomide are the most widely used immunomodulatory agents. Multiple mechanisms are involved in its anti-tumor activity, lasting from anti-proliferation, induction of apoptosis, modulation of bone marrow microenvironment, and immune modulating action. One of the standard treatment regimens for newly diagnosed multiple myeloma patients not eligible for transplantation is the combination of lenalidomide and dexamethasone (Rd) regimen [5]. Furthermore, its therapeutic effect is sometimes combined with other drugs, e.g., when combined with bortezomib (Vdregimen) or carfilzomib (KRdregimen), it has shown good effects in clinical trials. Second-generation immunomodulatory agents such as Pomalidomide share the same thalidomide and lenalidomide structure, but the latter inhibits the action of tumor cells more effectively. However, lenalidomide has a considerable response in patients with RRMM refractory to lenalidomide, equivalent to that of the high-dose dexamethasone regimen, but inferior to that of the pomalidomide and dexamethasone (Pd) regimen, with an objective response rate (ORR) and median PFS [6].

Apart from these categories, histone deacetylase inhibitors (HDACIs) have also revealed some potential in the chemical cure of multiple myeloma. The activity of HDACIs is inhibited by histone deacetylases, regulating the cell cycle progression, inducing apoptosis, and inhibiting angiogenesis. Combined with proteasome inhibitors or immunomodulatory agents in clinical trials, HDACIs also have synergistic anti-tumor effects. For instance, ORR and PFS were higher in RRMM patients in the combination of panobinostat with bortezomib and dexamethasone regimen [5].

Continuous new drugs and therapeutic strategies have resulted in new drugs in the treatment of multiple myeloma, and have discovery of the mechanistic pathophysiology of multiple myeloma. As a consequence, a new class of immunomodulatory agents referred to as CELMoD (Cereblon, E3 ligase, Macija, and Death domain) class drugs are being developed and have shown clinical activity in patients resistant to IMiD. Moreover, encouraging preliminary clinical trial results utilizing BCMA CAR-T cell therapy have been achieved as well [3]. As a new source of hope for multiple myeloma treatment, the new drugs and therapeutic strategies are closely considered.

2.2. Current status of clinical application of drug combination

The treatment of multiple myeloma in clinical practice has to be individualised according to the patient's situation. For induction therapy for newly diagnosed transplant suitable patients, the standard induction is with three drug combinations that include proteasome inhibitors and immunomodulatory agents, as with the VTD or VRD regimens[3]. The induction therapy regimens also rapidly reduce tumor burden and increase the rate of induction remission. Autologous stem cell transplantation (ASCT) usually requires maintenance therapy to prolong the progression-free survival of patients.

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Mostly lenalidomide and bortezomib or some other drugs are used for maintenance therapy regimens[4].

The typical regimen for newly diagnosed patients who are not suitable for transplantation is lenalidomide and dexamethasone (Rd). In addition, it was also recommended that carfilzomib, lenalidomide, and dexamethasone (KRd) regimen is given to that class of patients, as the regimen has shown to be more curative in clinical and radiological trials. There is a greater choice of which treatment regimen to use for the relapsed/refractory patients. The pomalidomide and dexamethasone (Pd) regimen proved adequate for patients refractory to lenalidomide[6]. Furthermore, the carfilzomib and dexamethasone (Kd) regimen and the daratumumab in combination with bortezomib and dexamethasone regimen are being used in clinical practice as well[7].

For the clinical application of drug combinations, the management of adverse reactions is an important issue. Peripheral neuropathy is, for example, caused by proteasome inhibitors, while hematological toxicity is caused by immunomodulatory agents. It is necessary to closely monitor the adverse reactions of patients in the treatment process, and appropriate changes shall be made in the treatment regimen based on the condition of the patient. At the same time, drugs are also accessible, and the economic burden is also applicable to patients. Although new drugs and combination therapies have good therapeutic effects in clinical trials, their high prices prevent them from being applied widely in clinical practice.

Drug combination regimens are making a considerable progress in clinical practice for multiple myeloma (overall). Reasonable selection and optimization of the combination regimens can improve remission rate and survival in patients, and enhance the quality of life in patients. More work is still needed, however, for more effective and safer treatment regimens to be developed so that hope can be brought to patients with multiple myeloma.

3. Mechanisms and research progress of different drug combinations

3.1. Combination of proteasome inhibitors and immunomodulatory agents

The proteasome inhibitor and immunomodulatory agent are two important classes of drugs in the therapy of human multiple myeloma, and the combination provides significant therapeutic effects. Bortezomib, carfilzomib, and ixazomib proteins, among others, are proteasome inhibitors that inhibit proteasome activity by preventing degradation of proteins in the cell, leading to the disruption of myeloma cells' normal physiology and initiation of apoptosis. Myeloma cells can be directly inhibited with proliferation on the one hand, and on the other hand, the body's immune system can be regulated to increase the ability of the immune cells to recognize and kill myeloma cells with immunomodulatory agents like lenalidomide and pomalidomide. The combination of the two agents works through the mechanism of synergistic (worse) effects on myeloma cells by different pathways. Proteasome inhibitors result in increased accumulation of proteins and activation of stress responses within myeloma cells, whereas immunomodulatory agents act to strengthen the immune system to clear the stressed cells, in addition to improving the therapeutic effects of proteasome inhibitors. Furthermore, immunomodulatory drugs can also improve the microenvironment of bone marrow so that myeloma cells no longer rely on the microenvironment, yet combination therapies of these drugs with proteasome inhibitors will further reinforce the efficacy. Proteasome inhibitors and immunomodulatory agents in combination have been widely used for treating multiple myeloma in clinical studies. One such example is the combo regimen of bortezomib, lenalidomide, and dexamethasone (VRD regimen), which has become one of the first-line treatments for multiple myeloma[3]. Studies indicate that this regimen markedly raises the complete remission rate and progression—free survival of patients. The good effect has also been found in the combination of carfilzomib and pomalidomide, combined with dexamethasone, in the treatment of

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relapsed/refractory multiple myeloma. There are also some problems with the combination of proteasome inhibitors and immunomodulatory agents, however. For instance, there are some adverse reactions, for example, thrombosis. Long-term use of these drugs may even result in the development of drug resistance. Consequently, close monitoring of the adverse reaction during clinical use is required, and the treatment regimen should be adjusted by the time by the patient's condition and tolerance. In conclusion, proteasome inhibitors in combination with immunomodulatory agents are opening new ideas and ways for the treatment of multiple myeloma. Further study for the future focuses on mechanisms of action yet to be determined and optimizing combination therapies to attain better efficacy and decreased incidence of potential adverse reactions, respectively.

3.2. Combination of monoclonal antibodies with other drugs

Multiple myeloma treatments using monoclonal antibodies are important because these antibodies may bind to antigens expressed on myeloma cells and kill these cells directly. Daratumumab is one of the most widely used monoclonal antibodies, with the CD38 antigen highly expressed on the surface of multiple myeloma cells. Therapeutic effect can be achieved when daratumumab is administered as monotherapy, but maximum efficacy can be achieved with daratumumab in combination with other agents. The following are the mechanisms of a combination of monoclonal antibodies with other drugs. Monoclonal antibodies can provide direct binding and recognition of the antigen on the surface of myeloma cells and mediate both antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) to directly kill the myeloma cells. Second, monoclonal antibodies can be conjugated with chemotherapeutic compounds, proteasome inhibitors, or immunomodulatory agents to exert synergy by multiple mechanisms and increase the sensitivity for myeloma cells. For instance, the combination of daratumumab with bortezomib, lenalidomide, and dexamethasone (DVRd) regimen has demonstrated a similar high remission rate and progression-free survival in multiple myeloma treatment [7]. Furthermore, monoclonal antibodies can be administered together with another novel drug, such as the BCL-2 inhibitor venetoclax. Daratumumab plus venetoclax appears to have much better therapeutic outcomes in those with multiple myeloma carrying the chromosomal abnormality, who have a specific “fused” protein in myeloma cells that venetoclax unleashes. These combined regimens have a simultaneous action on several key signaling pathways and overcome the shortfalls of monotherapy; they represent new treatment options for relapsed or refractory multiple myeloma patients. Clinical studies with other drugs combined with monoclonal antibodies have been promising. As such, one study was able to extend median progression-free survival in these patients to more than 1410 years with this combination regimen of daratumumab with proteasome inhibitors and immunomodulatory agents [8]. This research demonstrates the high therapeutic potential of such a combination with a monoclonal antibody and another drug. However, there are also downsides to the combination with other medications. For example, combination therapy is accompanied by an increase in the frequency of infections as well as thrombosis. Also, for some patients, expected therapeutic effects were not realized with combination therapy, which might be due to individual differences in patients and tumor cell heterogeneity. For that reason, treatment regimens will have to be individually formulated according to the specific condition of the patients, and it will be important to closely monitor the adverse reactions of patients in clinical application. Additional future research will explore the mechanisms of action of the monoclonal combination with other drugs and better combination regimens. As the pathogenesis of multiple myeloma becomes better understood, new targets and drugs will always be there, making more available options for the combination use of monoclonal antibodies. In summary, the prospect for improved survival rate and quality of life in patients with multiple myeloma is brought about by the combination of monoclonal antibodies and other drugs for use in treatment.

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4. Future prospects

4.1. Exploration directions for new drug combination regimens

Based on an extensive study on the pathogenesis of MM and the development of new drug technologies, the exploration of future drug combination regimens is diversified and precise. On the one side, the immune therapeutics have provided the much-needed new hope for multiple myeloma. For instance, CAR-T cell therapy is a good example, wherein the T cells of patients are genetically engineered to specifically recognize and attack cancer cells, and the key target in this therapy is BCMA (B cell maturation antigen). Expectation is that it will be combined with traditional drugs like PI and IMiDs for a synergistic effect in the future. Although PIs interfere with the proteasome activity of tumor cells, therefore proteins accumulate in tumor cells and activate apoptosis, IMiDs can regulate the immune systems in several ways that ultimately reinforce the immune response against tumors. Besides enhancing the direct killing effect on tumor cells, these drugs can also induce improvements in the tumor microenvironment and promote the infiltration and function of immune cells, so that the therapeutic effects could be further enhanced if the CAR T cell therapy were combined with these drugs. Other hand, drug combination regimens that target the tumor microenvironment are also of great concern. The tumor microenvironment of multiple myeloma is complex; it involves bone marrow stromal cells, extracellular matrix, cytokines, etc, which mutually interact to establish favorable growth, survival, and drug resistance conditions for tumor cells. While anti-myeloma drugs exist, future research can be on developing drugs that target the tumor microenvironment and combining them with current anti-myeloma drugs. For instance, some newly developed drugs to counter bone marrow stromal cells interrupt the bond between tumor cells and stromal cells, therefore impeding the nutritional supply and sheltering effects of tumor cells; some cytokines targeting drugs control the function of immune cells in the tumor microenvironment, resulting in a stronger immune response watching tumors. If we can achieve more effective control of multiple myeloma through this multi-target drug combination strategy, it will fundamentally change the tumor microenvironment. Moreover, individual treatment is also an important way of future drug combination exploration. As the technologies for gene detection have become more popular and affordable, it is now possible to type patients' genes and detect biomarkers for multiple myeloma. Through the genetic mutation analysis, the chromosomal abnormality, and protein expression level of patients, the sensitivity and drug resistance of the patients to the drug can be predicted, so that the most suitable drug combination regimens of the patients can be tailored. For example, specific genetic mutations in patients can select more targeted drugs for combination therapy, while more aggressive drug combination strategies can be adopted in advance for patients with high risk, to improve the therapeutic effect and increase the survival rate. The individualized drug combination regimen according to individual characteristics will significantly increase the precision and efficacy of the treatment, minimize the side effects of the treatment, and have much greater convenient survival benefits for patients with multiple myeloma.

4.2. Clinical application prospects of drug combination

The drug combination for multiple myeloma has wide clinical application prospects, and it can largely improve the patients's living quality and prognosis. Rational drug combination regimens are more likely to enhance the response rate and the extent of remission with a therapeutic effect. For instance, a combination of PIs and IMiDs substantially prolonged the PFS and OS from PIs or IMiDs alone [9]. Determined by continuous inclusion of new drugs and optimization of combination regimens, these indicators are expected to improve further in the future. For patients who have relapsed or refractory MM, a drug combination is likely to break through the therapeutic bottleneck. Through the

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use of drugs that act via different mechanisms, the drug resistance of tumor cells is overcome, and the tumor can be reactivated to make the immune system of the body act against the tumor, thereby providing more treatment pathways and hope for these patients. The clinical application accessibility is determined to increasingly benefit more patients with the further development of medical technologies and improved medical insurance policies. Yet, on the other hand, the new drug development and marketing speed has increased, which allows more effective drugs to end in clinical use as early as possible. However, with the advancement of drug production technologies and competition for the drug market increasing, the price of the drug will gradually decline, which in turn will lighten the financial burden of the patients. In addition, the medical insurance coverage adjustment and expansion will provide more patients with the opportunity to receive the treatment of drug combination therapy. For instance, there are examples of some provinces that already have taken some drugs for treating multiple myeloma in the medical insurance scope of reimbursement coverage, and it is expected that more types of drugs and corresponding reimbursement ratios will be further expanded in the future so that more patients may be able to afford the cost of drug combination therapy. In addition, the optimization of drug combinations will be favorable from the perspective of patient quality of life. Improved physical and psychological condition of patients would be the result of improving the therapeutic effect and reducing the side effects of treatment. For example, new drug combination regimens can damage less normal tissue of the patients and improve efficacy of the drug, and decrease treatment-related adverse reactions such as nausea, vomiting, and infections. That will help patients to continue their normal living and working during treatment and improve their living quality. Furthermore, when therapeutic effects have been improved and the survival has been extended, patients spend more time together with family and friends, enjoy life, which leads to a greater psychological comfort and support. In general, the application prospects of drug combinations for multiple myeloma clinical applications are very broad. Continuous exploration of new combination regimens, optimal use of treatment strategies, and improving clinical application accessibility are expected to lead to better therapeutic effects and living quality for the patients of multiple myeloma, and ultimately realize effective control and cure of the malignant tumor.

5. Conclusion

In conclusion, drug combination therapy for multiple myeloma has made remarkable progress. By combining proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, and other drugs, it can improve the complete remission rate, extend survival, and enhance patients' quality of life. However, challenges like drug interactions and adverse reactions remain. Future research should focus on exploring new drug combinations, such as combining CAR-T cell therapy with traditional drugs and targeting the tumor microenvironment. Additionally, individualized treatment based on genetic analysis holds great promise. With the continuous development of medical technology and the expansion of medical insurance coverage, drug combination therapy is expected to bring more hope to multiple myeloma patients.

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