Research Progress of Decitabine in the Treatment of Drug Resistance to Myelodysplastic Syndrome Based on the Information of Literature Database

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Abstract. Objective: To summarize the progress of drug resistance in the treatment of myelodysplastic syndrome with Decitabine. Methods: To review the mechanism of action of DAC, the mechanism of action of DAC in the treatment of MDS resistance and the treatment options after drug resistance based on the relevant literature from domestic database. Results: As the demethylated drug, Decitabine (DAC) can reverse abnormal DNA methylation and thus prolonging the survival time of patients with MDS. However, some studies have found that not all patients can benefit from it, and even some patients may develop drug resistance. However, the mechanism of DAC resistance is not clearly discovered. After DAC failed to treat MDS, demethylated drugs can be replaced in the treatment of some patients. Conclusion: DAC has a significant effect on MDS, but the drug resistance rate is relatively high. The mechanism of drug resistance is still unclear, which is worthy of close attention of clinicians. In-depth study on the mechanism of drug resistance can better prolong the patient's survival time and improve the patient's quality of life.

Keywords: Myelodysplastic Syndrome (MDS), Decitabine(DAC), Drug Resistance

Introduction

MDS is a group of heterogeneous diseases originated from hematopoietic stem cells with major manifestations in dyshaematopoiesis and ineffective hematopoiesis of abnormal hematopoietic stem cells, which then leads to pancytopenia, resulting in clinical manifestations of anemia, infection and hemorrhage. Consequently, high risk of transformation to acute myelogenous leukemia will occur. It has been found that epigenetic abnormalities, especially DNA methylation, are one of the important mechanisms of MDS.

1. Mechanism of Action of DAC

Epigenetics refers to the change of expression level of genes with nucleotide sequence of genes unchanged. DNA methylation and histone modification are the most frequently seen epigenetic mechanism leading to the abnormal expression of genes and cellular phenotypic change. Demethylated drugs (HMAs) mainly play a role by irreversibly inhibiting DNA methyltransferase
(DNMT), inhibiting DNA synthesis, promoting cell apoptosis and reversing abnormal DNA methylation. Mesenchymal stromal cells (MSCs) are the main components of bone marrow. They regulate the activities of hematopoietic cells closely related to the promotion of normal blood cell development or the survival and reproduction of metacrine. MSCs in bone marrow of patients with MDS have been verified the capability to accelerate the progression of MDS [1]. However, whether phenotypes of MSCs (MDS-MSCs) derived from MDS can be reversed or not becomes a potential target for MDS therapy. Current studies have shown that MDS-MSCs processed by DAC block the differentiation of activated T cells into regulatory T cells and thus reversing the inhibitory immune microenvironment induced by MDS-MSCs. The immunosuppressive microenvironment formed by aging MSCs plays an important role in the progression of MDS from low risk to high risk [2]. CD274 is a major ligand for programmed cell death, which is widely expressed in tissues and contributes to the formation of immunosuppressive microenvironment in MDS to protect malignant cells from immune destruction. The decreased expression of CD274 in DAC-treated MDS-MSCs may be the mechanism of impaired differentiation ability of activated T cells into regulatory T cells induced by MDS-MSCs.

2. Research Progress of Drug Resistance Mechanism of DAC

2.1. Increased Expression of Immune Checkpoint Pathway

As Immune Checkpoint Pathways (ICPs) such as PD-1 and PD-L1 are bound to receptors on T cells, and PD-1 is a T-cell immune checkpoint protein. The binding of PD-1 and ligand PD-L1 and PD-L2 can inhibit cell activation. Many cancer cells use the PD-1 pathway to evade the immune response by upregulating surface PD-1 proteins and inactivating T cells. Secondly, DAC can induce increased secretion of pro-inflammatory factors and interferon, and up-regulate the expression of PD-L1, inhibit the proliferation of T cells through the PD-1/PD-L1 pathway, hindering their differentiation into plasma cells, and inducing the apoptosis of T cells, so as to promote the growth of tumor cells.

2.2. Abnormal Expression of DDX43/H19/miR186 Axis

DDX43 [DEAD (ASP-Glu - Ala-ASP) box polypeptide 43, DDX43] is considered as a tumor-specific gene, which is related to malignant proliferation and drug resistance of tumor cells, and is considered as an ideal target molecule for cancer therapy. H19 is a long non-coding RNA, approximately 2.3kb in length. Abnormal expression of H19 has been found in solid tumors such as bladder cancer, breast cancer and liver cancer, and plays an important role in tumor growth. Multiple studies have reported that miR-186, as a tumor suppressor miRNA, affects tumor development by inhibiting tumor cell growth and regulating cell cycle. DDX43 can inhibit miR-186 and release H19, thus promoting tumorogenesis [3].

2.3. Acute Inhibition of p53

P53 is a transcription factor that regulates the expression of downstream target genes and is involved in cell apoptosis, cell cycle arrest, senescence, metabolic regulation and other cellular processes. In addition, p53 is endowed with the properties of maintaining genomic stability. Through these functions, p53 plays a central role in preventing tumorigenesis and progression. Loss of p53 function, whether in form of mutation, gene deletion or increased expression of negative regulatory factors, can lead to the occurrence of a variety of tumors. In addition, p53 mutations are associated with resistance to standard chemotherapy and poor prognosis in cancer patients. Studies have found that acute inhibition of p53 leads to its resistance to DAC, while long-term chronic inhibition of p53 increases its sensitivity to DAC in myeloid tumors [4].

2.4. Increased Ratio of Cytosine Deaminase/Deoxycytosine Kinase

Human nucleoside transporters (hNTs) can be divided into human balanced nucleoside transporters (hENTs) and human concentration nucleoside transporters (hCNTs). However, any abnormalities in
DAC transport and metabolism may lead to inadequate forms of activation and DNA/RNA binding, leading to drug resistance. Due to the different effects of DCK and CDA on cytosine analogue metabolism, some scholars [5] compared some genes related to DAC metabolism, including the expressions of hENT1, hENT2, DCK and CDA between those who responded to DAC and those who did not. The results showed that the primary resistance to DAC may be caused by the increase of CDA and the decrease of DCK in some patients with primary resistance.

3. Treatment Options after DAC Treatment Resistance

3.1. Allogeneic Hematopoietic Stem Cell Transplantation

Although DAC is recommended by many guidelines as a first-line treatment for MDS, drug resistance remains a problem that confuses clinicians and needs to be addressed urgently. At present, allogeneic hematopoietic stem cell transplantation (ALLO-HSCT) is the only possible method to cure MDS. For patients with drug resistance to DAC treatment, transplantation should be the first option if available. allo-HSCTt was a good choice after DAC resistance, with a median survival of 19 months for allo-HSCT patients, compared with 1.4 and 6.3 months in patients receiving only supportive care and conventional chemotherapy. Compared with other treatments, allo-HSCT can prolong the survival of patients. Currently, no prospective study has assessed the prognosis of transplant patients after DAC treatment failure, but a retrospective study has shown that the 3-year relapse-free survival rate is 23.8% [6], which is encouraging. However, after allo-HSCT, the survival time of MDS patients with TP53 mutation was significantly shorter and the recurrence was earlier than that of patients without TP53 mutation, regardless of any treatment measures. Therefore, the advantages and risks should be fully balanced before transplantation.

3.2. Replacement by Other Drugs

3.2.1. Therapy by new targeted drugs. Guadecitabine is a new generation of demethylated drugs with a long half-life and exposure ratio. It is a dinucleotide antimetabolite of DAC, which is related to deoxyguanosine. This may lead to the gradual release of DAC in both extracellular and intracellular and lead to prolonged exposure to DAC. The second phase of the study assessed the efficacy of high-risk MDS. Recently, the study results at phase II showed that among patients whose median response time is 32%, the CR + mCR and OS were close to [7] 8 months and 12 months.

3.2.2. Immunoregulatory therapy. Some studies [8] found that Pyrin-domain-containing 3 (NLRP3) rich in leucine repeat sequence is a congenital receptor complex, and the presence of pathogen molecular-related patterns will trigger NLRP3 to bind to the receptor, thereby mediating Caspase-1 activation and cytokine secretion. Caspase-1 activates the precursor of IL-1β that can lead to the production of inflammation or a specialized form of cell death, or both. Methylene blue can inhibit the function of NLRP3, so in the transfusion dependent low-risk MDS dominated by bone marrow inflammation and apoptosis, methylene blue adjuvant therapy can restore the effective hematopoiesis of MDS[9].

3.3. Chemotherapy

New chemotherapy regimens may be chosen after resistance to DAC treatment. After HMA failure, MDS patients were treated with intensive therapy, and the survival time was 8.9 months. Recently, a large number of MDS patients (n = 307) were treated with cytarabine plus anthracycline (7+3) and high dose cytarabine or nucleoside analogues after HMA failure, with OS of 10.8 months and ORR of 41% [10].

In conclusion, DAC has a significant effect on MDS, but the drug resistance rate is relatively high. The mechanism of drug resistance is still unclear, which is worthy of close attention of clinicians. In-depth study on the mechanism of drug resistance can better prolong the patient's survival time and
improve the patient's quality of life.

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