2. All-trans Retinoic Acid in the Treatment of Acute Promyelocytic Leukemia

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Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloblastic leukemia (AML), which is characterized by unique morphology and coagulopathy (1). Patients with APL represent a marked hemorrhagic diathesis caused by disseminated intravascular coagulation (DIC) and excessive primary fibrinolysis. Introduction of all-trans retinoic acid (ATRA) has been the major breakthrough in the treatment of APL (2). Although the drug target was demonstrated after clinical use, ATRA is currently recognized as the molecular targeted therapy directed at the chimeric protein generated by the specific chromosomal translocation. In the history of cancer treatment, ATRA is the first successful molecular targeted drug, which would be a model of the development of new molecular targeted agents for many other malignant tumors.

2. Acute Promyelocytic Leukemia

APL represents approximately 10% of adult AML. APL cells possess a large amount of azurophilic granules, which contain tissue factor, leading to DIC. APL cells also express high levels of annexin II that results in increased fibrinolytic activity. In patients with APL, cytotoxic chemotherapy often exacerbates the extreme bleeding diathesis such as intracranial hemorrhage, resulting in a relatively high rate of early mortality. APL cells in the vast majority of patients have a characteristic chromosomal translocation t(15;17) that produces the fusion gene consisting of promyelocytic leukemia (PML) and retinoic acid receptor α (RARα). PML-RARα retains critical domains of PML and RARα, and plays a key role in the pathogenesis of APL (3).

3. Molecular Mechanism of Action of ATRA

RARα is a member of the nuclear hormone receptor superfamily that acts as ligand-inducible transcriptional regulators (3). RARα requires heterodimerization with retinoid X receptor α (RXRα) in order to bind retinoic acid response element (RARE) located in the promoter regions of the target genes. Unliganded RARα is capable of binding RARE and represses transcriptions by association with corepressors including mSin3A, NcoR and SMRT. These corepressors recruit histone deacetylase (HDAC) complex, resulting in histone deacetylation that leads to transcriptional silencing. Binding of retinoic acid (RA) to RARα induces dissociation of HDAC complex and recruits coactivators such as p300/CBP, leading to histone acetylation and activation of transcription. One of the potential RA/RARα target genes is a transcription factor C/EBPε that is believed to play a role in myeloid differentiation (3).

In APL cells, PML-RARα binds RARE through DNA binding domain of RARα in a dominant manner. PML-RARα mediates transcriptional repression of RARα target genes by recruitment of corepressor, HDAC and DNA methyltransferase. Physiological dose of RA cannot dissociate HDAC complex, leading to a maturational block in myeloid differentiation, which is thought to be a first step of leukemogenesis (3). In contrast, pharmacological doses of ATRA trigger dissociation of HDAC complex and recruitment of coactivators. Moreover, ATRA induces degradation of PML-RARα and activates normal RARα and PML, resulting in differentiation of APL cells.

4. Treatment with ATRA in Newly Diagnosed APL Patients

In the late 1980s, investigators in Shanghai demonstrated that the vitamin A derivative, ATRA, could induce differen-
tiation in APL cells with resolution of the life-threatening coagulopathy and achieve a high complete remission (CR) rate (2). Early studies of ATRA documented a marked clinical efficacy in patients with both relapsed and newly diagnosed APL, indicating ATRA has no cross-resistance against chemotherapeutic agents (1, 2). However, a rapid increase of leukocytes is commonly seen, which is often accompanied by RA syndrome (RAS) (1). The RAS is associated with the increase of differentiated neutrophils that secrete inflammatory cytokines such as IL-6, IL-8 and TNFα. The RAS is primarily manifested by fever and respiratory distress followed by interstitial pulmonary infiltrates, weight gain, pleural or pericardial effusion, and renal failure. Furthermore, most patients who were treated with ATRA alone after achievement of CR have relapse (1, 2). Therefore, the combination of ATRA and cytotoxic chemotherapy has been incorporated in the front-line therapy for newly diagnosed APL.

In the Japan Adult Leukemia Study Group (JALSG) AML 87 and AML89 studies, event-free survival (EFS) in all evaluable patients who were treated with chemotherapy alone was 32% (4, 5). In the JALSG APL92 and APL97 studies, which included ATRA plus chemotherapy followed by consolidation chemotherapy, the 5-year EFS were 52% and 65%, respectively (4-6). In several multicenter trials, more than 90% of APL patients treated with ATRA plus chemotherapy achieve CR and approximately 60-70% of patients have EFS (1, 3). Non-cross resistance between ATRA and chemotherapeutic drugs appears to contribute to the significant improvement in EFS. However, several major clinical problems still account for treatment failure, including early death, death during consolidation, and disease relapse. It is of importance to prevent hemorrhage and RAS during induction, because primary resistance to ATRA is an exception in newly diagnosed APL with t(15;17) (3). Initial leucocyte count more than 10×10⁹/L is a significant unfavorable prognostic factor for EFS (3, 6). The optimal chemotherapy during induction and postremission in this high-risk group remains to be determined. Because of the excellent response with ATRA plus chemotherapy, stem cell transplantation generally is not indicated in the first CR but might be considered for the high-risk patients.

5. New Therapeutic Agents for Relapsed APL

About 15-25% of patients eventually relapse and are possibly refractory to further ATRA and chemotherapy (1, 3). In addition, second CR achieved with ATRA lacks durability. New retinoid Am80 developed in Japan has more potent differentiation abilities than ATRA in vitro. Am80 induced a second CR in approximately 60% of patients with relapsed APL after treatment of ATRA (1). The Ministry of Health and Welfare of Japan approved Am80 (Amnolake®) in April 2005.

In the 1990s, investigators from China reported that arsenic trioxide could induce CR in patients with APL (7). Since arsenic functions through mechanisms different from ATRA, arsenic can induce a CR rate of more than 80% in relapsed patients after treatment with ATRA (7, 8). Furthermore, US trials demonstrated that molecular remission, as measured by reverse transcription polymerase chain reaction of marrow specimens for PML-RARα transcript, was achieved in more than 80% of relapsed APL patients (8). In Japan, investigators in Hamamatsu University School of Medicine have used arsenic for relapsed APL patients and obtained a high CR rate. Arsenic trioxide (Trisenox®) was approved for the treatment of relapsed and refractory APL in October 2004.

Currently, arsenic is considered the first-line therapy for relapsed APL patients (1, 8). Since arsenic does not appear to completely eradicate leukemic cells, the best postremission therapy remains to be examined. The outcome of autologous stem cell transplantation in patients with second molecular remission after arsenic therapy was excellent. Although Am80, arsenic trioxide, and mylotarg (CD33 antibody conjugated with calicheamycin) are effective for relapsed patients, their schedule and benefit when combined with other therapies for newly diagnosed APL remain to be determined.

6. Conclusions

With the advent of ATRA, APL has provided the first example of successful molecular targeted therapy. Since ATRA alone induces no molecular remission in most patients, chemotherapy is indispensable in the treatment of APL. ATRA induced a relatively good outcome in elderly patients. In addition, ATRA has reduced medical costs by means of successful treatment with a low incidence of hemorrhages and infections. While ATRA is quite effective and has only a few side effects, RAS is a serious adverse effect during induction therapy. In addition, point mutations in the RA binding domain of PML-RARα induce resistance to ATRA in relapsed patients. Mutations in ATP binding regions of BCR-ABL were also found in patients with chronic myeloid leukemia refractory to imatinib mesylate. This mechanism of resistance is a potentially important problem in molecular targeted agents. The experience of ATRA should be exploited in the treatment of other cancers. On the basis of further understanding of molecular mechanisms, drugs specifically working on pathogenic molecules should be developed for other tumors.

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