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Commentary

Treatment of Acute Promyelocytic Leukemia with Molecular Target Therapy

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DESCRIPTION

Since the first description of Acute Promyelocytic Leukemia (APL) as the most malignant form of acute leukemia in 1957, several developments have paved the way for this disease to be the most curable leukemia in adults and change the cancer treatment paradigm. Bernard et al. pioneered APL therapy in 1973, demonstrating a striking sensitivity to daunorubicin that was likely due to significantly lower P-glycoprotein expression in APL cells compared to other subtypes of Acute Myeloid Leukemia (AML). The use of (all-trans retinoic acid) ATRA, a noncytotoxic differentiating drug widely regarded as the first differentiation therapy, has radically altered the management, outcome, and prognosis of APL. In 1986, ATRA was first used in clinical studies to treat APL. Then the randomized studies in numerous locations across the world have shown a rise in the CR rate, a decrease in severe adverse effects, and an extend of remission duration. ATRA in combination with anthracycline-based chemotherapy can achieve CR in 90-95% of APL patients and cure the disease in 70-75%. ATRA and chemotherapeutic agent combination therapy should now be considered standard treatment for APL. Huge efforts have been made over the last decade to understand the molecular genesis of APL as well as the mechanism of action of ATRA.

ATRA's mechanism of action is as follows:

- Binding of ATRA to RAR receptors causes degradation of PML-RAR protein *via* the ubiquitin-proteasome and caspase system, leading to the restoration of terminal differentiation of promyelocytes;
- *In vitro* or *in vivo* exposure of APL cells to ATRA induces relocalization of PML and restores the normal structure of PODs;
- As a result, the repression of transcriptional activation of target genes is relieved, and promyelocyte differentiation is restored. APL treatment with arsenic compounds is a successful example of acute leukemia apoptosis induction therapy. As_2O_3 exerts two effects on APL cells.

A higher concentration of As_2O_3 (0.5-1.0 M) induced apoptosis with typical morphological changes, DNA laddering on agarose gel electrophoresis, the appearance of an apoptotic peak on flow cytometric analysis, and increased expression of annexin V on the cell surface membrane, according to *in vitro* studies with NB4 cells. As_2O_3 can induce APL cells to partially differentiate along the granulocytic pathway at lower concentrations.

Several *in vivo* and *in vitro* studies have confirmed the synergistic effect of ATRA and As_2O_3. SIH completed the first clinical trial in 2001. The CR rate was the same as ATRA or As_2O_3 alone, but the median day to CR was just 26 days, and the OS and DFS were significantly better than ATRA or As_2O_3 alone.

In newly diagnosed APL patients, the timing and dose of As_2O_3 combined with ATRA must be confirmed. Several genetic and phenotypic characteristics of Acute Promyelocytic Leukemia (APL) blasts have recently been demonstrated. These include the PML/RAR fusion and the transcription co-repressor complex recruited at the promoters of target genes by the hybrid protein, intense and homogeneous expression of the CD33 antigen, and the absence of a multidrug resistance-related phenotype, as well as a frequently mutated and constitutively activated FLT3 receptor. Such genotypic and phenotypic features are targeted by agents currently in use in front-line therapy or at relapse (retinoid, As_2O_3, anthracyclines, and antiCD33 monoclonal antibodies), as well as new medicines, such as histone deacetylase and FLT3 inhibitors, that may find a place in future therapy.

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