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Jacobs Journal of Bone Marrow and Stem Cell Research

Review Article

Differentiation and Apoptosis inducing Therapy with High-dose Methylprednisolone for non-APL Acute Myeloblastic Leukemia

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Received: 10-22-2015

Accepted: 11-10-2015

Published: 11-16-2015

Abstract

Considerable progress has been achieved in the treatment of patients with acute promyelocytic leukemia (APL) by using retinoic acid and/or arsenic trioxide. However, it is generally considered that an effective agent which induces differentiation of myeloid leukemic cells has not been provided for the treatment of patients with other subtypes of acute myeloblastic leukemia (AML). On the other hand, several in vitro studies have shown that certain steroid hormons (dexamethasone, prednisolone, methylprednisolone) induce differentiation of some mouse and human myeloid leukemic cells to macrophages and granulocytes. We have also shown that short-course (3 to7 days) high-dose methylprednisolone (HDMP, 20-30 mg/kg) treatment can induce terminal differentiation of myeloid leukemic cells in children with APL and in other subtypes of AML (AML-M1, AML-M2, AML-M4 and AML-M7). HDMP has also been shown to induce apoptosis of myeloid leukemic cells in different subtypes of AML in vivo and in vitro. After short-course (3 to 7 days) HDMP treatment alone, in addition to rapid clinical improvements, decreases in blast cells in both peripheral blood and bone marrow and dramatic reductions in the size of myeloid tumors were observed. HDMP combined with mild chemotherapy increased the remission rate (87-89%) and improved the outcome of the patients.

In conclusion, addition of HDMP as a differentiation and apoptosis inducing agent to initial induction therapy will be a promising novel therapeutic approach for patients with non-APL AML.

Keywords: High-Dose Methylprednisolone; Differentiation; Apoptosis; AML; Non-APL AML; Myeloid tumor; Corticosteroids

Introduction

Acute myeloblastic leukemia (AML) is a malignant proliferation of immature myeloid cells which fail to differentiate to mature cells. The establishment of a cell culture system for the clonal development of hematopoietic cells by Sachs and co-workers in the early 1960s, provided the facilities of the demonstration that some mouse and human myeloid leukemia cells can be induced to terminal differentiation in vitro and differentiation inducers have been proposed as a promising treatment approach for patients with AML [1-3]. In early 1980s, in vitro studies have shown that retinoic acid (RA), a derivative of vitamin A was effective in inducing differentiation of human myeloid leukemic cell line (HL-60) into mature granulocytes [4,5]. Furthermore, RA has also been shown in vitro to induce differentiation of fresh leukemic

cells obtained from patients with acute promyelocytic leukemia (APL) [6]. Based on these in vitro studies, clinical trial by using all-trans retinoic acid (ATRA) was initiated in China in 1988 and therapeutic effects of ATRA have been shown in de novo and relapsed patients with APL [7]. In the first multicenter randomized studies, since event-free survival was found significantly better in patients who received ATRA combined with chemotherapy, this trial was stopped early at the end of 1992 and it has been considered that ATRA should be included in treatment protocols in all patients with APL [8,9]. Number of further clinical studies have shown that addition of ATRA to conventional chemotherapy has changed the poor outcome of this subtype of AML with cure rates, up to 74-80% in newly diagnosed patients [10-12].

Arsenic trioxide (ATO), which has been used for more than 500 years in traditional Chinese medicine, has been incorporated in the treatment of APL patients since 1996 [13]. ATO has also been shown to induce differentiation and apoptosis of APL cell line NB4 and fresh APL cells with t(15;17) dose-dependently [13,14]. The use of ATO also resulted in significant improvement in the outcome of refractory or relapsed and newly diagnosed patients with APL [11,12]. Given the success of differentiation therapy with ATRA and/or ATO only in APL patients, it has been considered that the use of differentiation therapy in AML patients other than non-APL will be an important therapeutic strategy. Unfortunately, until now in the literature it is generally reported that no effective agent has yet been provided for the clinical use in non-APL AML patients.

Corticosteroid-Induced Differentiation and Apoptosis of Myeloid Leukemic Cells in Vitro

On the other hand, since mid 1970s, a number of experimental studies have shown that corticosteroids (CSs, dexamethasone and prednisolone) are the most potent agents for inducing differentiation of mouse myeloid leukemia cells into mature macrophages and granulocytes in vitro [15-17]. Moreover, it has been reported that high-concentration of dexamethasone (Dex) caused complete arrest of mouse myeloid leukemic cell proliferation and prolonged the survival of mice bearing sensitive myeloid leukemic cells [18]. In further in vitro studies differentiation and/or apoptosis inducing effects of methylprednisolone (MP) or Dex on human primary AML cells [19,20] and on human myeloid leukemia cell lines (HL-60, U937, K-562, HIMeg and t(8;21)-positive Kasumi cells) have been demonstrated in a dose-dependent manner [21-25]. Various effects of CSs and other steroid derivatives on human and mouse myeloid leukemic cells were reviewed previously [26-28].

Historical Review on Differentiation and Apoptosis of Leukemic Cells in Patients with APL and Non-APL AML Treated with Short-Course High-Dose MP

The inital observation of the remarkable antileukemic effect of high-dose MP (HDMP) treatment began in 1987, in two children with AML and hypereosinophilia. MP (20-30 mg/kg) was given because of the severe respiratory symptoms due to pulmonary eosinophilic infiltration. Short-period after HDMP administration, dramatic clinical and hematological improvements were observed. These results encouraged us to use HDMP in a case with AML-M4 who did not respond to chemotherapy and in relapsed children with AML-M1and AML-M2 who had not received HDMP treatment previously. Remarkable clinical and hematological improvements were also observed in these children following HDMP treatment alone and we have suggested that the addition of short-course HDMP asan initial treatment to chemotherapy would be an important treatment approach for AML patients [29].

Based on the results in experimental studies on mouse myeloid leukemic cells with CSs, morphologic evidence of in vivo differentiation of leukemic cells to mature granulocytes has been shown in a 12-year old boy with AML-M4 who presented with an orbitaocular granulocytic sarcoma (GS) treated with HDMP alone in 1991[30]. Short-period after administration of HDMP, in addition to dramatic resolution of orbital mass, significant decrease in bone marrow (BM) blasts and CD34-positive cells were detected and BM aspirate revealed Auer bodies in various stages of maturing myeloid cells and in polymorphonuclear leukocytes indicated that they were derived from leukemic cells. In further studies, morphological and cell surface membran antigen changes associated with induction of differentiation of myeloid leukemic cells to granulocytes have also been demonstrated in children with APL, AML-M1, AML-M2 and AML-M4 treated with short-course (3 to7 days) HDMP [31,32].

Interestingly, in a case with 2,5-year old boy who was diagnosed with acute megakaryoblastic leukemia, 4 days after HDMP treatment, in addition to rapid hematologic improvements, BM examination revealed disappearence of undifferentiatied cells and fibrosis which was replaced by diffuse infiltration of immature cells which developed cytoplasmic bleps and appeared as megakaryocte like cells producing platelets [33]. Flow cytometric analysis of BM cells showed an increase in cells expressing CD42a antigen and marked decrease in cells co-expressing CD34/117 antigens consistent with maturation. Dex in a dose-dependent manner has also been shown by Song and Cheng, to suppress the clonal proliferation of a human megakaryoblastic leukemia cell line and interestingly, combination of Dex with RA showed synergistic effects on proliferation and differentiation of these cells in vitro [23]. Synergistic effect of CS and RA on differentiation of HL-60 cells to neutrophils has also been demonstrated by Bunce et al [34]. In addition, it has been reported that Dex did not inhibit RA-induced differentiation and proliferation of t(15;17) NB4 cells, but rather showed antiproliferative activity [35]. Interestingly, it has been demonstrated that the combination of MP and ATO has also synergistic effect on the differentiation of HL-60 cells [36].

CSs which are used extensively in the treatment of lymphoid malignancies, have been shown effective by inducing apoptosis (programmed cell death) of leukemic cells. Interestingly, short-course HDMP treatment has also been shown to induce apoptosis of myeloid leukemic cells in different subtypes of AML in vivo and in vitro [19,33,37]. Furthermore, in a case with chronic myelomonocytic leukemia, in addition to dramatic resolution of pleural effusion, analysis of pleural effusion 24 and 48 hours after HDMP treatment revealed numerous apoptotic cell death with marked increase in cells expressing CD95 antigen [38]. More recently, beneficial effects of initial therapy with Dex (10 mg/6 hours intravenously) have been reported by Moreau et al in patients with AML-M5 who had respiratory failure from leukemic pulmonary infiltration [39].

MP has also been shown to induce differentiation an apoptosis of AML cells (Kasumi-1) with a t(8;21) translocation in a dose-dependent manner by Corsello et al in vitro [24]. Moreover, treatment of Kasumi-1 cells and primary patient AML cells with MP revealed dramatic decrease of AML1-ETO protein expression in a dose-responsive manner. In addition, it was observed that MP had synergistic effect when combined with either cytosine arabinoside or daunorubicin in Kasumi-1 and SKNO-1 cells. Furthermore, a rapid decrease in Bcl-2 levels was detected after MP treatment in vitro [24].

Dex-induced apoptosis has also been demonsrated in Kasumi-1 and SKNO-1 cells with a t(8;21) translocation by Miyoshi et al. [40]. When these t(8;21)-positive AML cells were treated with Dex the number of viable cells decreased in a dose-dependent manner. Suppression of Bcl-2 by CSs in human and mouse myeloid leukemic cells observed in in vitro studies [24,41,42] might indicate the role of MP treatment at high-doses in inducing apoptosis of myeloid leukemic cells.

The Role of Short-Course HDMP Treatment in AML

During our long-term clinical studies, in addition to dramatic clinical improvements (resolution of bone pain, unexplained high fever and improved activities), significant decrease in both perpheral blood and BM blasts were observed in children with different subtypes of AML. After short-course (4 to 7 days) HDMP (20-30 mg/kg, orally in a single daily dose, not exceeding 1 g) treatment alone, marrow blast decreased below 5% in 12 (32%) out of 37 children evaluated [43]. HDMP combined with mild chemotherapy (cytosine arabinoside 3mg/kg and adriamycin 1mg/kg) raised the complete remission (CR) rate up to 84,6% (n=26) [44] compared with the CR rate of historical controls (62%) [45]. In our further studies with two different protocols, CR rates were 87 % (n=23) and 89 % (n=45) in newly diagnosed AML children who had no extramedullary infiltration. In these studies, by using intensive maintenance therapy, improved outcomes were achieved and 5-year disease-free survival rate was 44% and 36% respectively [43]. More interestingly, dramatic decreases in the size of extramedullary infiltrations (orbitaocular, gingiva, soft tissue, oral cavity, spinal) were detected 24 hours to 7 days after HDMP treatment alone. Therapeutic role of HDMP on the extramedullary infiltration and myeloid tumors in children with AML and myelodysplastic syndrome has been reported previously in detail [43, 46,47]. However, the optimal dosage of MP and its role in maintenance therapy should be evaluated in further studies.

The use of short-course (3 to 5 days) HDMP treatment has the additional important benefit of accelerating chemotherapy-induced leukocyte recovery by stimulating CD34-positive hematopoietic progenitor cells during induction and maintenance therapy [48-53]. In addition, at the begining of induction therapy, while the peripheral blasts decreased significantly, short-course (4 days) HDMP treatment resulted in rapid increase in peripheral blood T4+,T8+ T-cells and natural killer (NK) cells which might also contribute to rapid antileukemic effect of HDMP [54]. Pharmacological concentrations of MP has also been shown to rapidly induce differentiation of CD34-positive hematopoietic precursors to NK cell by Vitale et al [55].

The use of agents that induce differentiation and/or apoptosis has also been considered for the treatment of malignant disease and AML has been suggested as a model for differentiation therapy for other malignancies (56). Interestingly, several in vitro studies have shown growth inhibitory effects of CSs associated with apoptosis or morphological changes in some human cancer (lung, glioma, breast, ovarian, chondroma, osteosarcoma, melanoma) cell lines in a dose-dependent manner [57-63]. Furthermore, Dex has been shown in vivo to inhibit tumor growth significantly in murine osteosarcomas dose-dependently [64]. The potential therapeutic role of CSs at high-doses has also been suggested by these researchers for the treatment of some malignant disease.

Although, the exact mechanisms of CSs at high-doses in inducing differentiation and apoptosis are not clear they may be effective through complex mechanisms to target several antileukemic pathways in AML [21,24,25,41,42,65,66]. In addition to classical genomic effects, CSs at high-doses may also function via non-genomic pathways that can contribute to the rapid therapeutic benefits. Further studies will provide more information on the molecular mechanisms of high-dose CS effect in AML and it would also be interesting to evaluate whether HDMP could be effective to target and eliminate leukemia initiating stem cells.

Conclusion

Short-course HDMP treatment can induce differentiation and apoptosis of leukemic cells in patients with different subtypes of AML. Despite the results obtained in numerous preclinical and long-term clinical studies, it is disappointing that clinical

trials in AML patients by using HDMP with favourable responses are very few in the literature [67-70]. However, it is worth noting that addition of short-course HDMP as a differentiation and apoptosis inducing agent to induction chemotherapy will be a promising novel treatment approach for patients with non-APL AML and may also have a therapeutic role in some other malignancies.

Acknowledgements

I would like to thank all my colleagues who had valuable contributions during long-term clinical and laboratory studies as seen in the list of references of the published papers. I also thank all doctors, our nurses and technical personnel who cared for the leukemic children during long clinical follow-up period. I would like to acknowledge Department of Infectious Disease and Blood Bank for their support to AML patients.

Conflict of Interest

The author has no conflict of interest to disclose.

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