Hiçsönmez. Int J Stem Cell Res Ther 2016, 3:033
DOI: 10.23937/2469-570X/1410033
Volume 3 | Issue 1

International Journal of
Stem Cell Research & Therapy

ISSN: 2469-570X

Short Review: Open Access

Short-Course High-Dose Methylprednisolone Induces Differentiation and Apoptosis of Myeloid Leukemic Cells

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Abstract

Differentiation therapy with all-trans retinoic acid significantly improved the outcome of patients with acute promyelocytic leukemia (APL). Therefore, researchers are still exploring the possibility of differentiation therapy for patients with acute myeloblastic leukemia (AML) other than APL. On the other hand, based on *in vitro* experiments on induction of differentiation of mouse myeloid leukemic cells with certain steroid hormones, we have demonstrated that short-course (3 to 7 days) high-dose methylprednisolone (HDMP) treatment can induce terminal differentiation of leukemic cells in children with APL and in other subtypes of AML (AML-M1, AML-M2, AML-M4 and AML-M7). HDMP treatment has also been shown to induce apoptosis of myeloid leukemic cells *in vivo* and *in vitro*. The addition of HDMP to chemotherapy increased the complete remission rate to 89% and prolonged the duration of remission in newly diagnosed children with AML and improved the outcome of patients who had myeloid tumor. In conclusion, future studies with HDMP as an initial treatment combined with chemotherapy could provide important benefits for further improvements in the outcome of patients with AML and possibly, in patients with some other malignancies.

Keywords

High-dose methylprednisolone, Differentiation, Apoptosis, Acute myeloblastic leukemia, Myeloid tumor, Myeloid-derived suppressor cells, Glucocorticoids

Introduction

Acute myeloblastic leukemia (AML) is characterized by the accumulation of immature myeloid cells, which lose their ability to differentiate into normal mature cells. The initial observations of the possibility of treatment with agents which induce terminal differentiation of myeloid leukemic cells were made by Leo Sachs and co-workers for more than 4 decades ago [1]. Although, several compounds which can induce differentiation of myeloid leukemic cells have been shown *in vitro*, only the retinoic acid, a derivative of Vitamin A, was transformed into a clinical benefit for patients with acute promyelocytic leukemia (APL). Since 1991, when all-trans retinoic acid (ATRA) became available on the market for clinical use, number of studies have shown that addition of ATRA to conventional chemotherapy has changed the poor outcome of patients with APL [2,3]. For a long period of time, the use of agents which can induce terminal differentiation of leukemic cells has also been considered as an important approach for the treatment of AML patients other than non- APL.

Glucocorticoid-induced Differentiation and/or Apoptosis of Myeloid Leukemic Cells *in vitro*

Since mid 1970s, a number of experimental studies have shown that dexamethasone (Dex) and prednisolone are the most potent agents for the induction of differentiation of mouse myeloid leukemic cells into macrophages and granulocytes [4-6]. Furthermore, high-concentration of Dex has shown to complete arrest of mouse myeloid leukemic cell proliferation and also prolonged the survival of mice inoculated with sensitive M1 cells [7]. The effects of glucocorticoids (GCs) on human myeloid leukemic cells (HL-60) have been studied *in vitro*, in the early 1980s [8,9]. In further studies, differentiation and/or apoptosis inducing effects of Dex or metylprednisolone (MP) on different subtypes of primary AML cells [10-12], and on human myeloid leukemia cell lines (HL-60, U937, K-562, HIMeg and t(8;21) –positive Kasumi-1 and Skno-1 cells) have been shown in a dose-dependent manner [13-18]. Various effects of GCs on mouse and human myeloid leukemic cells were reviewed in detail previously [19-20].

Short-course High-dose Methylprednisolone Treatment Induces Differentiation and Apoptosis of Myeloid Leukemic Cells *in vivo*

We first observed remarkable antileukemic effects of GC in 1987, in two AML children who had received high-dose MP (HDMP, 20-30 mg/kg/day) for the treatment of severe respiratory symptoms due to pulmonary eosinophilic infiltration. Subsequently, HDMP alone has shown effective in the treatment of a patient with AML-M4 who did not respond to chemotherapy and also in relapsed children with AML-M1 and AML-M2 [21]. Sugawara et al have also reported a complete remission in a 17-year-old male who was resistant to chemotherapy by using MP at a dose of 20 mg/kg/day combined with granulocyte colony-stimulating factor [22]. In addition, Shimohakamada et al reported morphologic and cytogenetic remission in an adult patient with t(8;21)-positive AML and pneumonia, who was treated with HDMP alone [23].

Based on the experimental studies with mice, morphologic

Citation: Hiçsönmez G (2015) Short-Course High-Dose Methylprednisolone Induces Differentiation and Apoptosis of Myeloid Leukemic Cells. Int J Stem Cell Res Ther 3:033. doi.org/10.23937/2469-570X/1410033

Received: Mar 08, 2016: **Accepted:** May 24, 2016: **Published:** May 28, 2016

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evidence of *in vivo* differentiation of myeloid leukemic cells to mature granulocytes has been shown in a case with AML-M4 treated with HDMP alone in 1991 [24]. In our further studies, short-course (3 to7 days) after HDMP treatment, in addition to marked decrease in blast cells in both peripheral blood (PB) and bone marrow (BM) , morphologic and cell surface antigen changes by flow cytometric analysis associated with induction of differentiation of leukemic cells to granulocytes have been shown in children with different subtypes of AML (AML-M1, AML-M2, AML-M3, AML- M4 and AML-M7) [25-27]. Interestingly, platelet producing micromegakaryocyte-like cells were also detected after 6 hours incubation of BM cells obtained from a case with AML-M7 with high-concentration of MP (10^{-6} M) [11]. Furthermore, in preclinical study, MP-induced differentiation of AML cells (Kasumi-1) with t(8;21) translocation has also been reported in a dose-dependent manner by Corsello et al [17].

Moreover, they have demonstrated that treatment of Kasumi-1 and primary patient AML cells with MP revealed a dramatic decrease of AML1-ETO protein in a proteasome and GC receptor-dependent manner.

HDMP treatment has also been shown to induce apoptosis of myeloid leukemic cells *in vivo* and *in vitro* [28,11]. Short-period after HDMP treatment alone, the characteristic morphology of various stages of apoptosis in BM cells were detected by light and electron microscopic studies in a case with AML-M3 and AML-M4 in whom terminal differentiation of leukemic cells was also detected [28].

Interestingly, in addition to rapid resolution of pleural effusion due to infiltration of malignant cells in children with chronic myelomonocytic leukemia, examination of pleural effusion 24 and 48 hours after HDMP treatment revealed maturation of leukemic cells and numerous apoptotic cells with marked increase in cells expressing the CD95 antigen [29]. These results might indicate the possible role of HDMP treatment in inducing differentiation and apoptosis of myeloid leukemic cells also at extramedullary site. Remarkable reduction of PB blast cells associated with the apperance of apoptotic cells in PB, 6 hours after MP (20 mg/kg/day) treatment has also been reported in elderly patients with AML secondary to myelodysplastic syndrome (MDS) by Suzuki et al [30]. Furthermore, treatment with MP has been shown to induce a dose-dependent increase in apoptosis of Kasumi-1 cells and decreased the apoptosis suppressing Bcl-2 protein level [17].

Following the administration of short-course (4 to 7 days) HDMP (20-30 mg/kg at a single dose, orally, not exceeding 1 g/day) treatment, dramatic clinical improvements and marked decrease in PB and BM blasts were noted in children with AML. Marrow blasts decreased below 5% in 12(32%) out of 37 patients evaluated. Addition of short-course HDMP to chemotherapy increased the remission rate to 87% (n = 23) and 89% (n = 45) in newly diagnosed children with AML who had no extramedullary infiltration (EMI) and improved the outcome of the patients. 5-year disease-free survival rate was 44% and 36% respectively [31]. More importantly, administration of HDMP as a single agent resulted in remarkable decrease in the size of EMI and myeloid tumors in children with different subtypes of AML and MDS as well [31-33]. After HDMP treatment, dramatic improvements of myeloid tumors (orbital, spinal and abdominal) in children with AML-M2 and t(8;21) in an unexpectedly short period of time were also reported by others [34-36]. HDMP as an initial treatment combined with chemotherapy also improved the outcome of these children with the exception of patients who presented with gingival infiltration. Therapeutic role of short-course HDMP in patients who presented with EMI or myeloid tumor has been reviewed previously [31,37].

During our clinical study, short-course HDMP treatment was well tolerated without significant side effects and no life threatening events have occured [31]. However, in 25% of the 53 AML children evaluated, white blood cell count increased starting 24 hours and 3 days after administration of HDMP treatment, while PB blast cells have decreased significantly. The increase in leukocyte count was well controlled by the administration of cytotoxic drugs.

Unlike with cytotoxic agents, short-course (4 to 7 days) HDMP treatment has also an important role for the early recovery of chemotherapy-induced leukopenia by affecting on some hematopoietic regulatory cytokines and stimulating CD34-positive progenitor cells [38-40]. Pretreatment with short- course HDMP, before consolidation therapy, reduced the duration and severity of neutropenia in AML children [41]. Furthermore, HDMP treatment during induction therapy, resulted in rapid increase in PB T4+, T8+ and natural killer cells possibly by the stimulation of CD34+ cells which may contribute to antileukemic effects [42]. It has also been reported that pharmacological concentration of MP can induce rapid *in vitro* differentiation of CD34+ hematopoietic precursors to NK cells [43].

The use of agents that induce differentiation and/or apoptosis has also been considered as a potential therapeutic approach for the cancer patients. Several *in vitro* studies have shown antiproliferative effect of GCs, some were associated with findings of apoptosis or morphological changes in the human cancer (glioma, lung, ovarian, breast, chondrosarcoma, osteosarcoma, melanoma) cell lines [44-49]. In addition Dex has been shown *in vivo* to inhibit tumor growth significantly in murine osteosarcomas dose-dependently [50]. More recently, several researchers have indicated the important role of the eradication of myeloid-derived suppressor cells (MDSCs) in the treatment of cancer patients [51,52]. MDSCs are heterogenous immature myeloid cells which arise from BM progenitor cells at different stages of differentiation that can suppress T cell responses and support tumor invasion and metastasis. The use of short-course HDMP treatment might also provide the elimination of MDSCs by inducing apoptosis and/or differentiation of these cells into mature non-suppressive cells in patients with cancer. Interestingly, Dex treatment has shown *in vivo* inhibition of the mouse tumor (melanoma) growth and lung metastasis by the alteration of BM derived $CD11b^{+}$ myeloid cells [53].

Although, the factors involved in the mechanisms of MP effects at high-doses in inducing differentiation and apoptosis of myeloid leukemic cells are not well known, it may function via genomic and/or non-genomic pathways which initiate a variaty of signaling cascades and is effective through complex mechanisms to target several antileukemic pathways. In a few number of preclinical studies, it was demonstrated that MP at high-doses dramatically reduced AML1-ETO and Bcl-2 protein levels in t(8;21)-positive myeloid leukemic cells [17]. It was also reported that in leukemic cell lines (HL-60 and K-562), serine/threonine protein phosphatases and JAK/STAT pathways play an important role in the signaling pathways that induce differentiation and apoptosis following HDMP treatment [15,18,54]. MP may also exert inhibitory actions on leukemic blasts through the suppression of NF-kappaB [55]. In addition, it would be interesting to evaluate whether HDMP could have a therapeutic role targeting EZH2 histone methyltransferase which can promote leukemogenicity by promoting differentiation blockage in AML. Overexpression of EZH2 has been reported in patients with AML and EMI [56,57] and interestingly, synergistic anti-tumor activity of EZH2 inhibitors and GC receptor agonist has been shown in non-Hodgkin lymphoma cells in a preclinical study [58].

In conclusion, we believe that future clinical and laboratory studies with high-dose GCs will provide important benefits to further improvements in the outcome of patients with AML and possibly in patients with some other malignancies.

Conflict of Interest

The author has no conflict of interest.

Acknowledgements

I would like to thank all my colleagues who had valuable contributions in these studies as seen in the list of references of the published papers. I would also like to thank to all doctors, nurses and technical personnel who also made contributions during the clinical follow-up period of children with leukemia.

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