The effect of steroid on myeloid leukemic cells: The potential of short-course high-dose methylprednisolone treatment in inducing differentiation, apoptosis and in stimulating myelopoiesis

Gönül Hıcşönmêz ∗
Department of pediatric Hematology, İhsan Dogramacı Children’s Hospital, Faculty of Medicine, Hacettepe University, Ankara 06100, Turkey

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Abstract

Several in vitro studies have shown that dexamethasone (Dex) and prednisolone can induce differentiation of some mouse and human myeloid leukemic cells to macrophages and granulocytes. Based on in vitro experiments, we have shown that short-course (3–7 days) high-dose methylprednisolone (HDMP) (20–30 mg/kg/day) treatment can induce differentiation of myeloid leukemic cells in vivo in children with different subtypes of acute myeloblastic leukemia (AML) (AML-M1, -M2, -M3, -M4, -M7). We have also shown that induction of apoptosis of myeloid leukemic cells with or without differentiation is possible by short-course HDMP treatment. In addition, short-course HDMP treatment has been shown to be effective in accelerating leukocyte recovery, possibly stimulating normal CD34-positive hematopoietic progenitor cells. Addition of HDMP to mild cytotoxic chemotherapy (low-dose cytosine arabinoside (LD-Ara-c), weekly mitoxantrone and Ara-c or 6-thioguanine) increased the remission rate (87–89%) and improved the outcome of AML children. We believe that the results of our 17-year clinical experience will provide important benefits to AML patients.

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1. Introduction

Acute myeloblastic leukemia (AML) is characterized by the accumulation of malignant myeloid cells associated with an arrest in different stages of differentiation. In the early 1960s, the establishment of a cell culture system for the clonal development of hematopoietic cells by Sachs and co-workers [1,2] facilitated the demonstration that some mouse myeloid leukemic (M1) cells could be induced to differentiate into normal macrophages and granulocytes in vitro and in vivo [3–5]. Furthermore, it has been shown that human myeloid leukemia cells can also be induced to differentiate terminally into mature cells in vitro [6,7]. From these results, treatment with differentiation inducers has long been proposed as a promising approach for patients with AML [8–11].

The effect of various agents on the differentiation of myeloid leukemic cells has been extensively studied in vitro [9–11]. The potential effect on induction of differentiation of leukemic cells by retinoic acid (RA), a derivative of Vitamin A, was first demonstrated in cultured HL-60 cells and cells obtained from patients with acute promyelocytic leukemia (APL) [12,13]. The in vitro effect of RA was transformed into a clinical benefit for patients with APL by Huang et al. in 1988 [14]. Since 1991, when all-trans retinoic acid (ATRA) became available on the market for clinical use [15], numerous clinical trials have been conducted and it
has been confirmed that ATRA, as a differentiation inducer, is effective in patients only with APL [15–17]. Since 1996, arsenic trioxide (As$_2$O$_3$) has been incorporated in treatment of APL patients [18]. In vitro studies have shown that As$_2$O$_3$ induces differentiation and apoptosis of APL cell line NB4 and fresh APL cells with t(15;17) dose dependently [19]. Despite the success obtained in APL, the results obtained with ATRA or As$_2$O$_3$ in non-APL patients are not encouraging. For this reason enormous efforts have been made to provide effective differentiating agents for AML patients other than APL. Despite the fact that induction of differentiation has been shown to be possible with various inducers in vitro, it is generally considered that no effective agent has yet been provided for clinical use [9–11]. Patients suffering from other subtypes of AML are therefore still looking for a new differentiation-inducing agent which will improve their outcome.

2. The effect of steroid on myeloid leukemic cells in vitro

2.1. In mice

The initial observation of the steroid effect on the murine myeloid leukemia cell line was made by Lotem and Sachs in 1974 [20,21]. Subsequently, a number of their studies have shown that there are some clones of mouse myeloid leukemic cells that can be induced by certain steroid hormones (dexamethasone (Dex), prednisolone) to differentiate normally to mature macrophages and granulocytes in vitro [22–24]. Moreover, some stages of differentiation (induction of C3 and Fc receptors on the cell surface, phagocytosis and secretion of lysozyme) of mouse myeloid leukemic cells which were not induced by the macrophage-granulocyte inducer (MGI) have been induced by Dex [22,24]. Steroid hormones are considered among the most potent differentiating agents.

Subsequent experiments with steroids were carried out in mice by a Japanese group from the Saitama Cancer Center. They have also shown that Dex can induce differentiation of mouse myeloid leukemia cells in vitro and in vivo [25–30]. Abe et al. have also observed that the degree of cell differentiation in various markers (Fc, C3 receptors, lysozyme activity, formation of macrophage) induced by 12 iU/ml 1α,25 dihydroxyvitamin D$_3$ was nearly equivalent to that induced by 1 μM Dex [31]. In addition, changes in phospholipid composition and prostaglandin synthesis during differentiation of cultured mouse myeloid leukemia cells with Dex have been demonstrated [32–33]. Furthermore, with an increase in the concentration of Dex, a complete arrest of mouse myeloid leukemic cells has been observed [34]. Treatment with Dex at a certain dose was also effective in prolongation of the survival time of mice bearing sensitive myeloid leukemia cells [27,34]. Some other effects of steroid on mouse myeloid leukemic cells were reviewed in [35].

Recently, a novel 2-aminosteroid, 2-(4′-methyl-1-piperazinyl)-3α-hydroxy-5α-androstan-17-one), has also been shown to suppress proliferation, and to induce apoptosis and differentiation of the murine myelomonocytic leukemia cell line (WEHI-3B) toward mature macrophage-like cells in vitro in a dose-dependent manner; it has also been shown to down-regulate expression of c-myc mRNA in WEHI-3B leukemia cells [36]. In addition, a suppression of expression of c-myc protooncogene by Dex has been demonstrated during Dex-induced differentiation of mouse myeloid leukemic cells in vitro [37,38]. Administration of 2-aminosteroid, especially at a high-dose (20 mg/kg), decreased the blast cells in both the peripheral blood (PB) and the bone marrow (BM) of BALB/c mice burdened with WEHI-3B cells in vivo [36].

2.2. In human

The effects of steroid on human myeloid leukemic cells have been demonstrated in vitro by Brandt et al. and Sukbitz et al. in 1981 and 1982, respectively [39,40]. In these studies Dex was used to increase the number of chemotactic receptors in cultures of differentiating human myeloid HL-60 cells in a dose-dependent manner and to potentiate the morphological differentiation of HL-60 cells induced by N, N-dimethylformamide or N-dimethylsulfoxide. In addition, Dex has been shown to promote the chemotactic activity in differentiating HL-60 cells induced by RA and a human T-cell-derived lymphokine [41]. Moreover, Dex markedly enhanced the RA-induced differentiation of HL-60 cells to neutrophils [42]. Recently, it has been demonstrated that different signal transduction pathways are used during differentiation of HL-60 cells by methylprednisolone (MP) or As$_2$O$_3$ [43]. In contrast to As$_2$O$_3$, MP-induced granulocytic differentiation is related with serine/threonine protein phosphatases type 2A subunit upregulation. As with the RA, the combination of As$_2$O$_3$ and MP had also a synergistic effect on differentiation of HL-60 cells [41–43]. Recently, Dex has been shown to induce differentiation and inhibit proliferation of the human megakaryoblastic leukemia cell line (HIMeg) in a dose-dependent manner by Song and Cheng [44]. Interestingly, the synergistic effect of Dex and RA on the differentiation of HIMeg cells was also observed in this study. Moreover, in vitro experiments showed that Dex did not inhibit the RA-induced differentiation and proliferation of t(15;17) NB4 cells [45]. Rather, it showed antiproliferative activity. Interestingly, Nakamaki et al. in 1989 found that Dex at $10^{-6}$ or $10^{-7}$ M concentration induced differentiation of leukemia cells in vitro in 10 out of 17 patients with different subtypes of AML (AML-M2, -M4, -M5); they suggested that steroid can be used as the drug for differentiation induction therapy in AML [46]. A novel aminosteroid, 2-[4′-methyl-1-piperazinyl]-3α,17β-dihydroxy-5α-androstan-17-one, has been shown to induce differentiation of HL-60 cells dose dependently by He and Jiang in 1999 [47].
3. Clinical studies with high-dose methylprednisolone in children with AML

Our initial observation on the remarkable antileukemic effect of high-dose methylprednisolone (HDMP) began in 1987. Following the short period after the administration of HDMP (30 mg/kg), which was given to alleviate severe respiratory symptoms in two children with AML associated with hemophagocytosis, dramatic clinical and hematological improvements were observed. Subsequently, we demonstrated that HDMP is a very effective agent in inducing remission in a patient with AML-M4 who had not responded to conventional chemotherapy and in relapsed children who had not received HDMP previously [48]. These exciting findings encouraged us to use HDMP in newly diagnosed AML children as an initial treatment [48-50]. Significant hematologic improvements were also noted within 2 weeks of HDMP treatment. Based on these results, we have suggested that the use of HDMP when applied as an initial short treatment in childhood AML will be an useful approach [48–50].

3.1. Induction of differentiation of myeloid leukemic cells by short-course (3–7 days) HDMP treatment in vivo

Based on experimental studies with mice, in 1991 we first showed morphologic evidence of in vivo differentiation of myeloid leukemic cells to mature granulocytes in a case with AML-M4 treated with HDMP alone [51]. Subsequently, HDMP treatment has been shown to induce terminal differentiation of myeloid leukemic cells in children with APL [52] and other subtypes of AML (FAB AML-M1, -M2, -M4, -M7) [53-56]. In all patients, after the administration of short-course (3–7 days) HDMP treatment alone, marked decreases in blast cells in both PB and BM, associated with an increase in the number of maturing myeloid cells, abnormally nucleated giant cells and polymorphonuclear-like cells were observed. A leukemic origin of some of these mature cells in PB and/or BM was confirmed by the presence of Auer rods detected 3–7 days after initiation of the HDMP treatment. In addition to these morphologic changes, surface marker analysis by flow cytometric studies showed a decrease in the expression of hematopoietic progenitor cell antigens (HLA-DR, CD117, CD34) and an increase in cells expressing mature myeloid cell antigens (CD14 and CD15). Furthermore, in some patients, during short-course (3–7 days) HDMP treatment detection of an increase in the percentage of aberrant cells co-expressing CD15/CD117 antigens also suggested the leukemic origin of these maturing myeloid cells [53-55]. More recently, we have demonstrated the potential effect of short-course HDMP treatment on the maturation of leukemic cells in a case with acute megakaryoblastic leukemia (AMKL) [56]. After 4 days of HDMP treatment a marked decrease in PB blast cells and an increase in platelet count were observed. These were associated with a striking changes in BM morphology. Furthermore, flow cytometric analysis of BM cells 4 days after HDMP treatment demonstrated a decrease in the percentage of cells co-expressing CD34 and CD117 antigens and a marked increase in CD42a antigen. These striking changes in BM morphology and immunophenotype suggest the potential effect of HDMP on the maturation of megakaryocytic leukemic cells. Interestingly, in our previous in vitro study, platelet-producing micromegakaryocyte-like cells were also detected after 6 h incubation of BM cells obtained from another case with AMKL with 10^{-8} M MP [57].

3.2. Induction of apoptosis of myeloid leukemic cells by short-course HDMP treatment in vivo

Since suppression of apoptotic cell death has been implicated in playing a significant role in leukemia [58,59], pharmacological manipulation by induction of apoptosis of leukemic cells has been suggested as another promising approach to the treatment of patients with leukemia [59,60]. Glucocorticoids (GCs), which are used extensively in lymphoid malignancies, have been shown to induce cell death by apoptosis by Robertson et al. in 1978 [61]. The lethal effect in the human myeloid leukemic cell line (RUS2) can also be achieved in vitro with doses of GCs which greatly exceed physiological and pharmacological levels by Bird et al. in 1977 [62]. Apoptosis has been demonstrated to be the common mode of cell death of differentiated human myeloid leukemic cells. HL-60 cells and the myelomonocytic leukemia cell line P39 differentiated by RA in vitro have been shown to die via apoptosis [63,64].

We have also shown that induction of apoptosis in myeloid leukemic cells with or without differentiation is possible by HDMP [57,65]. Following short-course (4 days) HDMP treatment the characteristic morphologic variability for various stages of apoptosis in BM cells has been shown by light and electron microscopic studies in two children with AML-M3 and M4 in whom terminal differentiation of leukemic cells was also detected [65]. More interestingly, 4 days after HDMP treatment complete resolution of pleural effusions, due to infiltration of malignant cells, were observed in two children with chronic myelomonocytic leukemia [66]. In addition, 24 and 48 h after HDMP treatment, examination of pleural aspirate revealed numerous apoptotic cells with a marked increase in cells expressing the CD95 antigen. We have also shown in vitro that 24 and 48 h after the addition of both low (10^{-8} M) and high (10^{-5} M) concentrations of MP to freshly obtained BM leukemic cells from four (three AML-M1 and one AML-M7) of nine AML children resulted in a dose-dependent increase in apoptotic cells [57]. Matsubara et al. have also observed that myeloid leukemic cells obtained from AML patients undergo apoptosis when treated with prednisolone (10 μmol/l) in vitro [60]. In addition, Dex-induced apoptosis has been demonstrated in an AML cell line with a t(8;21) chromosome translocation by Miyoshi et al. in 1997 [67]. The suppression of the oncogene bcl-2 by Dex might have a role in inducing apoptosis of myeloid leukemic cells [37].
Despite the fact that the response to glucocorticoids is thought possibly to be mediated by the high affinity GC receptors which have been identified in human leukemic myeloblast and in HL-60 cells [39,44,68–70], the mechanisms of the action of HDMP in inducing differentiation and apoptosis of myeloid leukemic cells are not clearly defined. However, it seems that several factors other than steroid binding to receptors may play a role in the induction of differentiation and apoptosis of myeloid leukemic cells [37,38,43].

In addition, the optimal therapeutic dosage of MP to induce differentiation and apoptosis is unknown. However, previous [71–73] and our clinical studies and in vitro experiments in both human [44,57,62,67] and mice [30,34] indicate that steroid at high doses is effective on myeloid leukemic cells. It is hoped that further studies will allow us to provide detailed information about the effectiveness of HDMP.

Recently, we have shown that administration of a short-course (4 days) of HDMP at the beginning of induction therapy can result in a significant increase in PB T-lymphocytes expressing CD3, CD4, CD8 CD45RA and CD16 + 56 (natural killer) cells which may contribute to the antileukemic effect of HDMP [74].

3.3. Stimulation of myelopoiesis by short-course HDMP treatment

Although significant progress has been made with intensive chemotherapy protocols, the overcoming of their suppressive effect on normal hematopoietic cells is another important approach for the treatment of leukemic patients. Recombinant hematopoietic factors have been shown to be very effective in shortening chemotherapy-induced neutropenia. However, there are some limitations on their use in AML, since they can also stimulate the proliferation of leukemic cells [75]. In addition their high cost is also another important factor.

Leukocyte recovery has been obtained in patients with aplastic anemia and myelofibrosis who were treated with HDMP [76,77]. Moreover, restoration of normal hematopoiesis was also reported with short-course HDMP treatment (30 mg/kg/day, for 3 days) in patients with refractory anemia [78].

In 1991, we first demonstrated that short-course (3–5 days) HDMP treatment significantly shortened the leukopenic period in children with acute lymphoblastic leukemia (ALL) who had no infection [79]. Subsequently, the beneficial effect of short-course (4 days) HDMP treatment for the acceleration of leukocyte recovery has been demonstrated during maintenance and induction therapy in neutrophenic children with AML [80,81]. The increase in leukocyte counts following short-course HDMP treatment has been shown to associate with an increase in both BM and PB CD34+ hematopoietic progenitor cells [80–83]. This increase in CD34+ cells was found to be significantly higher than that obtained in patients who received standard dose (2 mg/kg) steroid treatment [83].

The increase in leukocyte count and in CD34-positive cells has been shown to be possibly associated with its stimulatory effect on the granulocyte-colony-stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor and its inhibitory effect on negative regulators of hematopoiesis, such as tumor necrosis factor alpha and/or gamma-interferon [84,85]. In addition, the possibility of an inhibitory effect of steroid on the production of leukemia associated inhibitory factor (LAI) from human myeloid leukemic cells, which has a suppressive effect on normal hematopoietic cells, should be considered [86]. From the results of these studies, we have been successfully using short-course (3–5 days) HDMP to shorten chemotherapy-induced neutropenic period in leukemic children who had no infection.

More recently, we have shown that administration of short-course (4 days) HDMP before high-dose consolidation therapy is effective in reducing the duration and severity of neutropenia in children with AML [87]. Our clinical results confirmed the findings which were recently reported by Wang et al. [88]. They have also shown that pretreatment with Dex before cytotoxic chemotherapy prevented a decrease in granulocyte count in mice in a dose-dependent manner. In addition, Kriegler et al. have shown that Dex at high doses increases the BM progenitor cells and PB neutrophils during cytotoxic chemotherapy in mice [89]. Pretreatment with ATRA has also been reported to accelerate polymorphonuclear recovery after chemotherapy in patients with APL [90].

3.4. Clinical trials with HDMP

In our earlier study, very few children received MP intravenously (i.v.). Since oral administration of MP has been found to be as effective as the i.v. route [91], since 1989, patients with no infection have received MP sodium succinate (Prednol-L, MN pharmaceutical, Turkey) orally at a single daily dose of 30–20 mg/kg (not exceeding 1 g/day), after breakfast, together with an antiacid. Following the administration of HDMP alone, dramatic clinical improvements such as improved activities, resolution of bone pain and unexplained high fever were noted within 24 or 48 h in almost all patients. In addition, a marked decrease in the size of enlarged livers and spleens were observed [48,92]. Massive doses of steroid have also been used in patients with AML, mostly before 1960, and beneficial clinical and hematological effects have been described in a few patients [71–73].

3.5. The effect of short-course HDMP alone on bone marrow blasts and extramedullary infiltration

In order to evaluate the effect of HDMP on blast cells and extramedullary infiltration, initial treatment was begun with HDMP alone and then cytotoxic chemotherapy was added. Short-course HDMP treatment resulted in a rapid decrease in both PB and BM blast cells [48–56,81,82,92,93]. Four to seven days after HDMP alone, the effect of HDMP on BM blasts was evaluated in 37 children. Marrow blasts dropped below 5% in 12 of 37 (32%) children, below 15% in 20 (54%)
and below 25% in 27 (73%) [93]. In addition, HDMP as an initial treatment has been shown effective for AML patient with hypoplastic BM at presentation [94].

Marked reductions in PB and BM blast cells were also observed in relapsed children who had not received HDMP previously [48]. Decreases in marrow blasts ≤15% were detected in four out of five (80%) relapsed patients 2 weeks after HDMP treatment alone. This effect was not obtained in patients who had previously been exposed to HDMP. However, we have observed that 3–4 months after discontinuation of HDMP treatment, patients responded to HDMP.

Following the administration of HDMP as a single agent, dramatic improvement of extramedullary infiltrates (Orbitaocular, gingiva, soft tissue, pleura) have been observed in different subtypes of AML children [49,55,92,93,95] and in children with myelodysplastic syndrome as well [66,96]. In some cases its remarkable effect, especially on orbital granulocytic sarcoma, has been detected starting 24 or 48 h after HDMP treatment and orbital mass disappeared clinically within 4–7 days in most of the patients [55,95]. The effect of HDMP on extramedullary infiltration has been discussed in detail in [93]. As we have demonstrated in the malignant cells of pleural effusion, HDMP treatment can induce differentiation and apoptosis of leukemic cells at extramedullary sites as well [66]. HDMP seems to hold promise as an effective drug for patients with extramedullary infiltration.

3.6. The effect of combined HDMP with cytotoxic chemotherapy

Outlines of the treatment protocols of our two different studies have been reported previously [92,93]. In both studies, patients also received short-course (5 days) HDMP during maintenance therapy. In our first study, reported in 1992, a total of 26 newly diagnosed children were entered and 22 (88.4%) achieved complete remission (CR) [92]. This was significantly higher when compared with the results of the historical group (62%) treated by chemotherapy (adriamycin and Ara-c) alone [97].

In our subsequent study reported in 2004, HDMP was combined with mild cytotoxic therapies (low-dose cytosine arabinoside (LD-Ara-c), weekly mitoxantrone and Ara-c or 6-thioguanine) in two different protocols [93]. Here the CR rate was 87 and 89% for the 68 children who had no extramedullary infiltration. The 4-year disease-free survival (DFS) rates (±S.E.) were 44 ± 12 and 35 ± 8%. These results may support the findings reported by Waxman et al. [98]. From the results of their study, they have suggested that combination cytotoxic-differentiation therapy may provide reductions in the amount of chemotherapeutic agents while increasing their therapeutic effect. However, further studies should evaluate whether the addition of HDMP to more intensive therapy than used in our studies, will increase CR and DFS rates in AML.

4. The effect of high-dose steroid in children with ALL

The remarkable antileukemic effect of HDMP obtained in AML encouraged us to use HDMP in children with ALL refractory to conventional chemotherapy and in relapsed patients [99]. CR was achieved within 3 weeks with HDMP alone or combined with very mild cytotoxic chemotherapy (Ara-c and/or 6-thioguanine) in six out of the 24 (25%) patients. Successful results with HDMP (1 g/m²) alone in the treatment of central nervous system infiltration, BM and testicular relapse of children with ALL also reported by Ryalls et al. [100]. Combined HDMP with cytotoxic chemotherapy improved the outcome of newly diagnosed ALL children who had unfavorable presenting features [101]. Schwartz et al. have also described better initial response by using high-dose Dex (18 or 150 mg/m²/day, for 3 days) in high-risk ALL children [102]. These results were confirmed with randomized study using high and conventional-dose steroid therapy in high-risk ALL children [103]. Recently, it has been demonstrated that administration of Dex provides a better event-free survival for children with ALL [104–107]. In further studies the optimal dosage of steroid and its role in maintenance therapy should be evaluated in ALL as well.

5. The side effects of HDMP

During 17 years of clinical experience, we have noted that HDMP related toxicity is mild and no life threatening events have occurred [92,93]. HDMP administration is well tolerated without significant side effects. However, a few patients developed a mild cushingoid appearance, mild hypertension, hyperglycemia, bradicardia, arrhythmia, myalgia, abdominal pain and liver enlargement with mild elevation of liver enzymes. All of these were resolved after discontinuation of HDMP. Previously, MP at doses of 15–30 mg/kg/day, and even much higher doses, have been used in various hematologic conditions without major adverse effects [71,73,76,77,108]. It is worth noting that when high-dose steroids have been administered in a single dose as used in our study, a lower rate of serious side effects were also noted by others [76,77,100,108] possibly due to rapid clearance of the steroid.

5.1. HDMP-induced leukocytosis

We have observed that while PB blast cells have decreased significantly (P < 0.05), the white blood cell (WBC) count increased starting 24 h and 3 days after administration of HDMP in some cases [52–54,93]. Changes of WBC count between 4 and 7 days of HDMP treatment alone were evaluated in 53 AML children [93]. A significant elevation of WBC count was observed in 13 of 53 (25%) cases. None of the patients developed RA-like syndromes and the increase was well controlled by the administration of cytotoxic drugs. In contrast, WBC counts decreased in 33 (62%) children.
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References


A rapid increase in WBC count following high-dose steroid has also been noted by others as the acceleration of AML [2,10]. However, we observed that this increase was not associated with the increase in blast cells. Although the pathogenesis of short-course HDMP-induced leukocytosis developed in some AML patients is unclear, it might be related to stimulation of normal CD34-positive hematopoietic progenitor cells [80–83].

Subsequent to the demonstration of the in vitro differentiation effect of retinoids on HL-60 cells, a number of clinical studies were reported confirming that retinoids are also effective in vivo in patients with APL. Unfortunately, there are only two reports in the literature describing the CR in adult patients with AML, which is disappointing. By using HDMP combined with G-CSF, CR was described in a case with refractory AML by Sugawara et al. in 1991 [110]. In another adult patient, who had pneumonia and was treated with HDMP, CR associated with cytogenetic remission has been reported by Shimobakamada et al. in 2001 [111].

In summary, short-course (3–7 days) HDMP treatment has been shown to induce differentiation and apoptosis of myeloid leukemic cells in children with different subtypes (AML-M1, -M2, -M3, -M4, -M7) of AML. In addition, short-course (3–5days) HDMP accelerates leukocyte recovery, possibly associated with stimulation of normal CD34+ hematopoietic progenitor cells. Administration of short-course HDMP alone was associated with a rapid decrease in the number of PB, BM blasts and in the size of extramedullary infiltration. Addition of HDMP to cytotoxic chemotherapy increased the remission rate and improved the outcome of the patients. We believe that the results obtained in experimental studies with steroids both in mice and in human myeloid leukemic cells, and the results from our 17-year clinical studies will provide important benefits for the outcome of patients with AML and possibly for patients with other malignancies.


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