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Myeloprotective Effect of Short-Course High-Dose Methylprednisolone Treatment Before Consolidation Therapy in Children With Acute Myeloblastic Leukemia

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In our previous studies, short-course high-dose methylprednisolone (HDMP) has been shown to shorten the chemotherapy-induced neutropenic period by stimulating the $CD34^+$ hematopoietic progenitor cells in children with acute leukemia. In this study, we investigate the role of short-course HDMP on induction of a myeloprotective effect when administered before consolidation therapy consisting of high-dose cytosine arabinoside and daunorubicin. Thirty-four consecutive newly diagnosed children with acute myeloblastic leukemia (AML) who received 64 courses of consolidation regimen were entered into the study. The patients received HDMP (group A) at a daily dose of 30 mg/kg methylprednisolone starting 4 days before the initiation of consolidation therapy. The control group did not receive HDMP (group B). There were no differences in the white blood cell (WBC) and absolute neutrophil counts (ANC) between group A (at day –4) and group B (at day 0) at the beginning of the study (medians: 3×10^9/L vs. 3.2×10^9/L and 1.5×10^9/L vs. 1.7×10^9/L, respectively). The WBC count increased significantly from 3×10^9/L to 6.4×10^9/L, and ANC increased from 1.5×10^9/L to 3.9×10^9/L after 4 days of HDMP treatment in group A ($P < 0.01$). Following high-dose chemotherapy, the median values of WBC and ANC also remained higher than the control values during the 16 days of the follow-up period. The neutropenic period was significantly shorter in the HDMP group than in the control group (9 ± 5.2 days vs. 22 ± 4.7 days) ($P < 0.05$). The duration of hospitalization and the interval between two chemotherapy cycles were significantly decreased in group A when compared group B (9 ± 2.7 vs. 14 ± 2.7 days; 22 ± 4.7 vs. 26 ± 4.2 days, respectively) ($P < 0.05$). Moreover, following consolidation therapy, the number of patients with ANC values below 0.5×10^9/L was lower in group A when compared the group B. In conclusion, the administration of short-course (4 days) HDMP before high-dose chemotherapy has been found to be beneficial for reducing the duration and severity of neutropenia. Further studies with short-course HDMP are required to evaluate its myeloprotective effects in patients with other malignancies. Am. J. Hematol. 80:1–5, 2005. © 2005 Wiley-Liss, Inc.

Key words: high-dose methylprednisolone; acute myeloblastic leukemia; children; consolidation therapy; neutropenia

INTRODUCTION

Over the past two decades, considerable progress has been made in the treatment of acute myeloblastic leukemia (AML) with intensive chemotherapy and bone marrow transplantation. Furthermore, post-remission therapy consisting of high-dose cytosine-arabinoside (HD Ara-C) have been shown to produce a significant impact on the outcome of these patients [1,2]. However, therapy-related myelotoxicity is one of the challenging risk factors for morbidity and mortality. In addition, chemotherapy-induced myelosuppression may prevent the administration of the chemotherapeutic agents on

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the treatment schedule, which can also adversely affect the clinical outcome. Therefore, recombinant human hematopoietic growth factors (rh-GFs) are widely used in chemotherapy-induced neutropenia to restore normal hematopoiesis [3,4].

On the other hand, high-dose methylprednisolone (HDMP) which induce differentiation and apoptosis of myeloid leukemic cells has also been shown to stimulate $CD34^+$ hematopoietic progenitor cells in children with acute leukemia during remission induction and maintenance therapy [5–8]. Therefore, instead of rh-GFs we have been successfully using short-courses (3–5 days) of HDMP to shorten the chemotherapy-induced neutropenic period in leukemic children with no recent infection [8,9].

In this study, we investigated the possible myeloprotective effects of short-course HDMP treatment administered before the consolidation therapy consisting of HD Ara-C and daunorubicin in children with AML.

PATIENTS AND METHODS

Between April 1995 and October 2002, 34 consecutive newly diagnosed children with AML who achieved remission were included in this study. Patients' ages ranged from 1.5 to 16 years (17 boys and 17 girls) at the time of diagnosis. After achieving remission, all patients received 3 or 4 courses of consolidation regimen according to our institutional chemotherapy protocols [10]. Each course consisted of cytosine–arabinoside at a dose of 1 g/m^2/day intravenously for a 2-hr infusion for 3 days and weekly daunorubicin (30 mg/m^2) for 2 doses. All patients were admitted to the hospital during the consolidation therapy, and none of them had a sign infection.

Patients were classified into two groups. In group A, patients received HDMP before consolidation therapy. Patients in group B did not receive HDMP or placebo. After informed consent had been obtained, short-course HDMP was given randomly before administration of every other course, for a total of 64 consolidation therapies. Thirteen of the 34 patients participated both in group A and in group B. Patients received methylprednisolone sodium succinate (Prednol-L) orally at a single daily dose of 30 mg/kg (not exceeding 1 g/day) in the morning starting 4 days before the initiation of consolidation therapy (day −4) and was continued for 4 days until day 0. The white blood cell (WBC) counts and absolute neutrophil counts (ANC) were determined on days −4, 0, 4, 7, 10, 13, and 16 after the initiation of consolidation therapy. In addition, patients who had severe neutropenia were further followed for the evaluation of the duration of the neutropenic period, which was defined by the number of days from the day of ANC $\leq 0.5 \times 10^9$/L until the first day with an ANC $> 0.5 \times 10^9$/L. The total hospital days of each course and the time interval between two chemotherapy cycles (from the beginning day of consolidation regimen to starting the next chemotherapy cycle scheduled) were evaluated in both groups A and B.

Statistical Analysis

Statistical comparison was performed using the SPSS statistical program. The Mann–Whitney *U*-test was used for independent samples and χ^2 or Fisher's exact χ^2 test were used to compare means and frequencies.

RESULTS

The effect of short-course HDMP treatment on the number of WBC and ANC in AML patients is shown in Table I. There was no significant difference in the baseline values of WBC and ANC between group A (at day −4) and group B (at day 0). The median WBC counts significantly increased from 3×10^9/L to 6.4×10^9/L and ANC from 1.5×10^9/L to 3.9×10^9/L after 4 days of HDMP treatment in group A ($P < 0.01$) (Table I).

The WBC and ANC counts decreased after the initiation of HD Ara-C and daunomycin in both

TABLE I. Changes of the Median Values (Range) of Peripheral Blood WBC and ANC in Children With AML Following High-Dose Chemotherapy

	WBC ($\times 10^9$/L)			ANC ($\times 10^9$/L)		
Day	Group A (HDMP(+))	Group B (HDMP(−))	*P*	Group A (HDMP(+))	Group B (HDMP(−))	*P*
−4	3.0 (1.2–6.0)	—	—	1.5 (0.2–4.0)	—	—
0	6.4 (2.0–17.6)	3.2 (1.5–6.0)	< 0.01	3.9 (1.3–15.5)	1.7 (0.5–4.5)	< 0.01
4	4.5 (1.2–9.6)	2.8 (0.8–6.2)	< 0.01	3.1 (0.7–7.3)	1.4 (0.3–4.6)	< 0.01
7	2.6 (1.1–6.2)	2.0 (0.3–6.4)	< 0.05	1.6 (0.2–4.8)	0.9 (0.02–4.6)	< 0.05
10	2.1 (0.6–4.9)	1.2 (0.3–2.9)	< 0.01	0.8 (0.05–2.4)	0.4 (0–2.1)	< 0.05
13	1.9 (0.6–4.3)	1.2 (0.4–3.5)	> 0.05	0.5 (0–2.2)	0.2 (0–2.2)	> 0.05
16	1.5 (0.6–8.6)	1.4 (0.3–5.0)	> 0.05	0.6 (0–4.4)	0.1 (0–2.2)	< 0.01

groups. However, following high-dose chemotherapy the median values of WBC and ANC in the HDMP group remained higher than the control values during the 16 days (Fig. 1). The difference for WBC counts was found to be statistically higher on days 0, 4, 7, and 10 in patients who received HDMP. ANC values were also found to be significantly higher on days 0, 4, 7, 10, and 16 in the HDMP group (Table I).

As seen in Fig. 2, following high-dose chemotherapy the number of children with ANC $\leq 0.5 \times 10^9$/L was found to be lower among patients who received HDMP when compared to the patients who did not receive it. This difference at day 10 and day 16 was significant ($P < 0.05$).

The neutropenic period was significantly shorter in the HDMP group than in the control group (9 ± 5.2 vs. 22 ± 4.7 days) ($P < 0.05$). The duration of hospitalization and the interval between two chemotherapy cycles significantly decreased in group A when compared to group B (9 ± 2.7 vs. 14 ± 2.7 days; 22 ± 4.7 vs. 26 ± 4.2 days, respectively) ($P < 0.05$). HDMP treatment was well tolerated, as observed in our previous studies. Short-course HDMP-related, very mild toxicity (abdominal pain, hypertension, myalgia) was observed rarely, and no life-threatening events have occurred. Following the consolidation therapy, the incidence of infection observed in the HDMP-treated group (52%) was not different from that in the control group (66%).

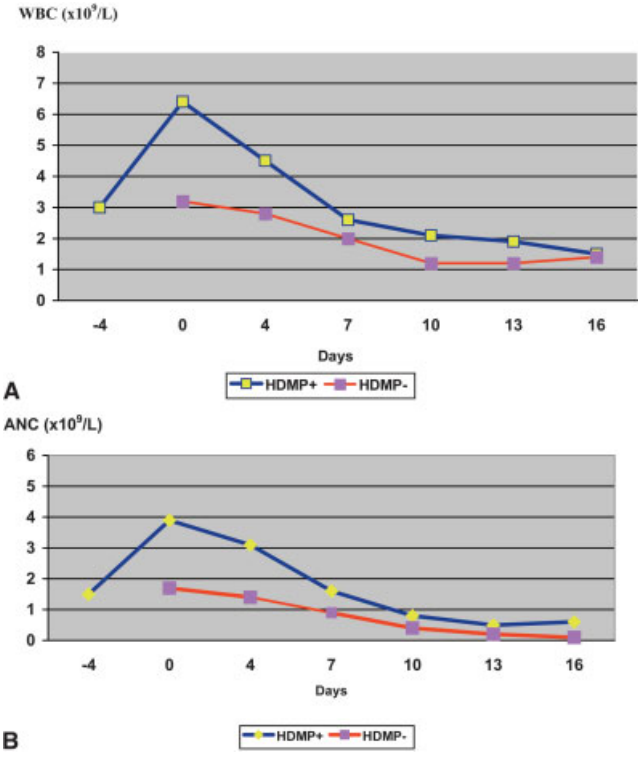

Fig. 1. Following high-dose chemotherapy: (A) changes in median WBC values of HDMP(+) and HDMP(–) groups; (B) changes in median ANC values of HDMP(+) and HDMP(–) groups. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

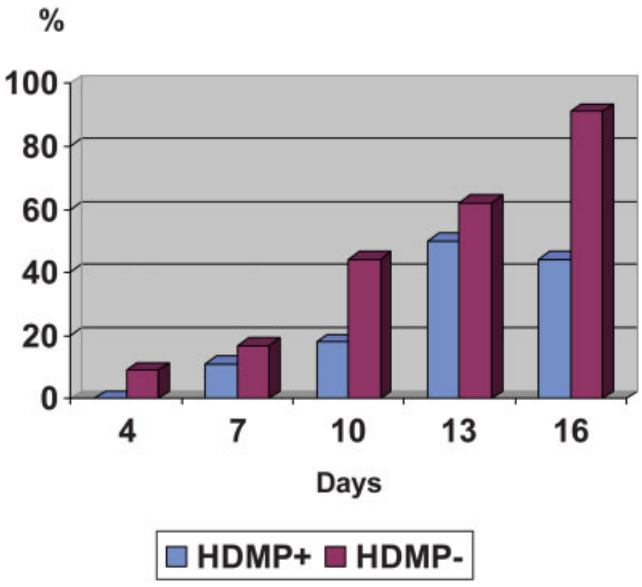

Fig. 2. Comparison of the percent of patients with ANC ≤ 0.5×10^9/L after high-dose chemotherapy. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

DISCUSSION

Favorable effects of intensive chemotherapy on treatment of AML has been demonstrated in previous studies [1,2]. Considering the suppressive effect of high-dose chemotherapy on normal bone marrow cells, the rapid restoration of hematopoiesis is an other important approach for the treatment of these patients.

The rh-GFs are widely used for prevention of chemotherapy-induced neutropenia and restoration of normal hematopoiesis [3,4]. However, there is a growing concern regarding the use of hematopoietic growth factors in patients with AML because of the expression of growth factor receptors in most myeloid leukemic cells that may potentially induce blastic proliferation [11]. The requirement of a parenteral route of administration (intravenous or subcutaneous) and their high cost are other limitations of rh-GFs.

On the other hand, retinoic acid, a differentiation inducer, has also been shown to stimulate normal hematopoiesis in in vitro studies [12,13], and pretreatment with *all-trans*-retinoic acid has been described to accelerate polymorphonuclear cell recovery after chemotherapy in patients with promyelocytic leukemia (APL) [14]. In contrast to retinoic acid, which induces

differentiation of leukemic cells in patients with APL alone, HDMP treatment has been shown to induce terminal differentiation of leukemic cells in children with different subtypes of AML (FAB AML M1, M2, M3, M4, M7) [15–17]. Several studies in mice have also been shown that certain steroid hormones (dexamethasone and prednisolone) are among the most potent agents that induce differentiation of myeloid leukemic cells [18].

It was first demonstrated that short-course (3–5 days) HDMP can accelerate leukocyte recovery in children with ALL following chemotherapy-induced leukopenia by Hiçsönmez et al. [9]. Since then, beneficial effects of HDMP to shorten the chemotherapy-induced neutropenia have also been demonstrated during maintenance therapy in children with AML [8]. Short-course HDMP during the early phase of induction therapy in children with ALL and AML has been shown to increase peripheral blood PMNL cells and decrease peripheral blood and bone marrow blasts. These were associated with an increase in $CD34^+$ hematopoietic progenitor cells, possibly by stimulating granulocyte-macrophage colony stimulating factor as well as granulocyte-colony stimulating factor and by decreasing tumor necrosis factor-α and interferon-γ [5–7,19]. The increase in $CD34^+$ cells in patients treated with short-course HDMP was found to be significantly higher than that obtained in patients who received conventional doses of steroid therapy (2 mg/kg) [5,6]. Furthermore, in vitro studies have demonstrated the inhibitory effect of steroids on the production of the leukemia-associated inhibitor from human myeloid leukemic cells, which can have a suppressive effect on normal progenitor cells [20]. Besides its significant antileukemic effects which effected prognosis, stimulation of normal myelopoiesis by short-course HDMP treatment is an additional advantage for the treatment of patients with AML. In contrast, several studies have shown that there is little or no effect of G-CSF/GM-CSF on the outcome of AML patients. Thus short-course HDMP treatment is used in patients who have no infection rather than rh-GFs at our institution with the low cost advantage.

In this study, we have observed that pretreatment with short-course HDMP significantly prevented the decrease in WBC and ANC following high-dose chemotherapy (Table I). In addition, a lower number of patients suffered from very severe neutropenia ($ANC \leq 0.5 \times 10^9/L$) among patients who received HDMP treatment (Fig. 2). These results showed that short-course HDMP before high-dose chemotherapy is also beneficial for reducing the duration and severity of neutropenia. Moreover, the duration of hospitalization significantly decreased in patients who received HDMP, which may also result in reduction of treatment costs. Therefore, such a therapeutic treatment approach may be suggested to play a beneficial role in other hematologic and nonhematologic malignancies. Although the long-term effect on the outcome has not been documented in this study, patients who were given HDMP before consolidation received their chemotherapy protocol in a less interrupted manner. Because the number of patients is limited in the present study, further studies of larger series may provide more information about this important treatment approach and may be used to stimulate normal hematopoietic progenitors before autologous bone marrow transplantation as well.

Kriegler et al. have shown that dexamethasone administered at high doses increases the number of BM progenitor cells and PB neutrophils during cytotoxic chemotherapy in experimental studies, and they suggest that the use of corticosteroids during cancer therapy be reconsidered to obtain maximum benefit [21]. Our clinical results also supported the very recently reported findings of Wang et al., who have shown that pretreatment with dexamethasone before cytotoxic chemotherapy prevented a decrease in granulocyte count in a dose-dependent manner in mice [22].

In conclusion, the current study suggests that the use of short-course HDMP before high-dose chemotherapy may be a promising approach for the treatment of patients with AML. Further studies evaluating the myeloprotective efficacy of short-course HDMP in other high-dose chemotherapy protocols will provide useful information for the treatment of cancer patients.

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