

High-dose Glucocorticoid for the Treatment of Myeloid Sarcoma

Gonul Hicsonmez*

Faculty of Medicine, Department of pediatric Hematology, Hacettepe University, Ankara 06100, Turkey

Abstract

Myeloid sarcoma is a tumor of myeloblast or poorly differentiated myeloid cells that can occur in extramedullary sites, as isolated tumor, concomitantly with or after the diagnosis of acute myeloblastic leukemia. Despite considerable improvement achieved in the outcome of patients with acute myeloblastic leukemia by using intensive chemotherapy and/or hematopoietic stem cell transplantation, it is generally considered to be poor in patients with myeloid sarcoma. The aim of this review is to indicate the potential therapeutic effects of high-dose glucocorticoid treatment which induce differentiation and apoptosis of myeloid leukemic cells, as a new treatment approach for patients with myeloid sarcoma. We have shown that short-course (3 to 7 days) high-dose methylprednisolone treatment that might also induce differentiation and apoptosis of leukemic cells in the extramedullary sites resulted in dramatic decreases in the size of myeloid sarcoma in children with or without marrow infiltration. From the results of our long-term clinical studies, we suggest that to use short-course high-dose glucocorticoids combined with intensive chemotherapy protocol would be a promising treatment strategy for patients with myeloid sarcoma. However, in further studies, the prognostic significance of different localization of myeloid sarcoma and the long term effect of the addition of high-dose glucocorticoid to intensive AML chemotherapy protocols should be explored in larger series.

Keywords: Myeloid sarcoma; High-dose glucocorticoid; Methylprednisolone; Differentiation; Apoptosis; AML

Myeloid sarcoma (MS) also referred as granulocytic sarcoma or myeloblastoma is a rare extramedullary (EM) tumor of myeloblasts or poorly differentiated myeloid cells. It could be the initial presenting clinical feature with or without bone marrow infiltration in patients with acute myeloblastic leukemia (AML) and may occur in patients with myelodysplastic syndrome (MDS) or in accelerated phase of chronic myelocytic leukemia. However, diagnostic and therapeutic approach to patients presented with MS is a challenging issue as recently reviewed in detail [1,2]. Due to the lack of uniform criteria for definition of MS according to the inclusion of involved sites of EM infiltration of leukemic cells, a wide range of MS incidence has been reported both in adults (1.8-9%) [1-4] and in children (7-18%) [5,6]. In our series, among 127 previously untreated children with AML excluding the EM infiltration in gingiva, central nervous system, lymph nodes, skin and pleura, the frequency of MS was found to be 21% and the orbita is the most commonly involved site with the 10% incidence [7].

Although, the prognostic importance is controversial, the outcome of patients presented with MS is generally considered to be poor both in adults and in children [1,4,8-12] especially, in patients who developed MS after hematopoietic stem cell transplantation (HSCT) [13,14]. However, effective treatment strategy is not clear and currently recommended treatment regimen for patients with MS with or without bone marrow involvement is to use intensive AML chemotherapy protocols. Although, the role of radiotherapy on survival is not clear, the results of several studies revealed that addition of radiotherapy to chemotherapy or surgical removal of leukemic mass has no effect on the outcome, but, these may be indicated for the relief of symptomatic complications of tumor mass [1,4,5,10,12]. Some retrospective studies have shown superior outcome in adult patients with MS who underwent allogeneic or autologous HSCT [10,15,16]. Recently, an alternative therapeutic approach by using targeted therapy with tyrosine kinase inhibitor (TKI, imatinib) or anti-CD33 monoclonal antibody (gemtuzumab ozogamicin) has been reported with some beneficial effect in limited number of patients with MS [17,18]. Therefore, patients are still awaiting for development of new treatment strategies.

On the other hand, the use of agents that can induce differentiation and apoptosis of myeloid leukemic cells would be a promising treatment approach for patients with MS. Various *in vitro* studies both in mice and in human myeloid leukemic cells revealed that glucocorticoids (GCs) at high-doses can induce differentiation and/or apoptosis of leukemic cells as reviewed previously [19-21]. We first demonstrated in 1991, morphologic evidence of terminal differentiation of myeloid leukemic cells in a boy with AML-M4 who presented with orbitaocular MS treated with high-dose methylprednisolone (HDMP, 20-30 mg/kg/day, not exceeding 1 g/day) orally in a single dose. In addition to the rapid decrease of blast cells in both peripheral blood and in bone marrow short-period (4 days) after its administration, the decrease in the size of orbital mass was unexpectedly, very striking [22]. In our further studies, dramatic reductions in the size of orbital mass were also detected in non-leukemic [23] and AML children following 24 hours to 4 days after HDMP treatment [7,24]. Interestingly, remarkable decreases in the size of EM infiltration of leukemic cells in other sites (gingiva, oral cavity, spinal, soft tissues and pleura) were also noted short-period after initiation of HDMP as a single agent, in children with AML and MDS, even in patients who had no significant hematologic improvements [7,25]. Dramatic decreases in orbital, abdominal and spinal mass, following 3 to 7 days of HDMP treatment were also reported by others in a child with AML-M2 and t(8;21) and in children who had no marrow infiltration. Imaging studies, computerized tomography and magnetic resonance, also disclosed the important reductions in the size of tumor mass [26,27]. Marked

*Corresponding author: Gonul Hicsonmez, M.D, Retired Professor, Department of pediatric Hematology, Hacettepe University, Erdemkent Sitesi, Ardic Sok. No.19, UmitkOy, Ankara 06000, Turkey, Tel: +90-312-2381119; Fax: +90-312-3105700; E-mail: gsonmez@hacettepe.edu.tr

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decrease of orbital granulocytic sarcoma and improved paraparesis due to epidural thoracic MS, 24 hours after initiation of methylprednisolone (MP, 30 mg/kg) treatment alone was also detected in a case with AML-M2 and t(8;21) translocation by Takeda et al. [28]. Although, the presence of MS is mostly occurred in patients with AML-M2 and t(8;21), it is important to note that HDMP was also effective treatment for MS when occurred in children with different subtypes of AML [7]. Moreover, in adult patient with AML or in patients without marrow infiltration, significant improvements of cutaneous leukemic infiltrations, intestinal or intracranial granulocytic sarcoma were also detected following short-course steroid treatment (without indicating dosage) alone [29-32]. More interestingly, in addition to significant improvement of respiratory disorders, we have demonstrated complete resolution of pleural effusions and marked decrease in pericardial effusion in children with chronic myelomonocytic leukemia 4 days after HDMP treatment alone, that also induced differentiation and apoptosis of malignant cells in the pleural effusion [33]. Matsushima et al. also described a case with MDS in whom pericardial and pleural effusions disappeared following HDMP (20 mg/kg/day) treatment [34]. Very recently, it has been reported that addition of dexamethasone (Dex, 10 mg/6 hours) to chemotherapy decreased early mortality rate, the incidence of respiratory deterioration and the need for ventilatory support of adult patients with AML-M5 who had lung infiltrates of leukemic cells [35].

We have shown that terminal differentiation of leukemic cells is possible in children with different subtypes of AML (AML-M1, M2, M3, M4, M7) treated with short-course (3 to 7 days) HDMP [36-38] which can also induce apoptosis of myeloid leukemic cells with or without differentiation *in vivo* and *in vitro* [39,40]. Dramatic selective blast cell reduction associated with apoptosis and improved outcome has been reported by Suzuki et al. [41] in elderly patients (63-89 years) with AML secondary to MDS treated with MP (125 mg/body) alone [41].

The use of agents that induce differentiation and/or apoptosis has also been considered to be a potential therapeutic approach for the cancer patients. Interestingly, several *in vitro* studies have also shown the growth inhibitory effects of GCs (Dex, MP) in some human malignant tumor cell lines in a dose-dependent manner and to induce apoptosis or differentiation of malignant cells [42-46]. From the results of these *in vitro* studies, the authors indicated the possible potential therapeutic effect of high-dose GC treatment for some other types of malignant tumor.

Although, the optimal dosage of MP and its duration is not clear, addition of HDMP to cytotoxic chemotherapy increased the remission rate and prolonged the duration of remission of our patients with AML [7]. Improved outcome was also observed in our small number of AML children with MS who achieved remission with HDMP and chemotherapy and received post induction therapy with high-dose cytarabine [7] and also in children with MDS and MS [25]. However, this improvement was not noted in children who initially had gingival infiltration. Bisschop et al. [6] also reported that children who presented with gingival infiltration had poor prognosis compared to those who presented with MS [6].

The translocation of t(8;21) is associated with AML-M2 phenotype and give rise to AML1-ETO fusion protein which inhibit differentiation of immature progenitors to mature neutrophils. MP has also been shown by Corsello et al. [47] *in vitro* to induce differentiation and apoptosis of AML cell lines with a t(8;21) translocation in a dose-dependent manner. They have also demonstrated that treatment of

t(8;21)-positive Kasumi cells and primary patient AML cells with MP revealed dramatic decrease of AML1-ETO protein in a dose and time responsive manner [47]. In addition, it was also shown that MP had synergistic effect with either Ara-c or daunorubicin on the leukemic cell viability. More recently, Joha et al. [48] reported that restoration of GC- induced leucine zipper protein (GILZ) expression which is modulated by GCs, overcome TKI resistance in human and mouse myeloid leukemic cells expressing BCR-ABL by inhibiting mTORC2/AKT signaling pathway [48]. They have demonstrated that, treatment of TKI resistant BCR-ABL+ cells obtained from relapsed chronic myeloid leukemia patients with Dex followed by imatinib resulted in apoptosis dose-dependently. These results may suggest the possible potential effect of GCs at high doses targeting mTORC2 in other subtypes of AML. Dex has also been shown to down regulate the expression of the anti-apoptotic oncogene Bcl-2 in human and in mouse myeloid leukemic cells [47-49] and suppress the expression of c-myc protooncogene during Dex-induced differentiation of mouse myeloid leukemic cells *in vitro* [50]. Furthermore, Xu et al. [51] also demonstrated that Dex may down regulate the expression of FLT3 (FMS-like tyrosine kinase 3) receptor in some myeloid leukemic cells obtained from patients with AML, *in vitro* [51]. The results of these *in vitro* studies indicate that HDMP treatment may also suppress the expression of these apoptosis- and differentiation- inducing genes in some patients with AML. Despite, the factors involved in the exact mechanisms of GC effects at high-doses in inducing differentiation and apoptosis remains unclear, it may be effective through complex mechanisms to target several other antileukemic pathways [52-54].

In conclusion, since early response to treatment is an important prognostic factor, addition of short-course high-dose GCs as a potential targeted therapy to AML intensive chemotherapy protocols, would be a promising treatment approach for patients with MS. However, long-term effects of high-dose GCs on different localization of MS should be explored in larger randomized series.

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