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High-dose Glucocorticoid for the Treatment of Myeloid Sarcoma

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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 to7 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 thyrosine 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

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decrease of orbital granulocytic sarcoma and improved paraparesis due to epidural thorasic 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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References

1. Bakst RL, Tallman MS, Douer D, Yahalom J (2011) How I treat extramedullary acute myeloid leukemia. Blood 118: 3785-3793.
2. Avni B, Koren-Michowitz M (2011) Myeloid sarcoma: current approach and therapeutic options. Therap adv in Hematol 2: 309-316.
3. Neiman RS, Barcos M, Berard C, Bonner H, Mann R, et al. (1981) Granulocytic sarcoma: a clinicopathologic study of 61 biopsied cases. Cancer 48: 1426-1437.
4. Lan TY, Lin DT, Tien HF, Yang RS, Chen CY, et al. (2009) Prognostic factors of treatment outcomes in patients with granulocytic sarcoma. Acta Hematol 122: 238-246.
5. Jenkin RD, Al-Shabanah M, Al Nasser A, El-Solh H, Al sudairy R, et al. (2000) Extramedullary myeloid tumors in children: the limited value of local treatment. J Pediatr Hematol Oncol 22: 34-40.
6. Bisschop MM, Revesz T, Bierings M, van Verden JF, van Wering ER, et al. (2001) Extramedullary infiltrates at diagnosis have no prognostic significance in children with acute myeloid leukaemia. Leukemia 15: 46-49.
7. Hicsonmez G, Cetin M, Tuncer AM, Yenicesu I, Aslan D, et al. (2004) Children with acute myeloblastic leukemia presenting with extramedullary infiltration: the effects of high-dose steroid treatment. Leuk Res 28: 25-34.
8. Byrd JC, Weiss RB, Arthur DC, Lawrence D, Baer MR, et al. (1997)

Extramedullary leukemia adversely affects hematologic complete remission rate and overall survival in patients with t(8;21)(q22;q22): results from Cancer and Leukemia Group B 8461. J Clin Oncol 15: 466-475.

9. Paydas S, Zorludemir S, Ergin M (2006) Granulocytic sarcoma: 32 cases and review of the literature. Leuk Lyphoma 47: 2527-2541.

10. Avni B, Rund D, Levin M, Grisariu S, Ben-Yehuda D, et al. (2012) Clinical implications of acute myeloid leukemia presenting as myeloid sarcoma. Hematol Oncol 30: 34-40.

11. Cavdar AO, Babacan E ,Gozdasoglu S, Kilicturgay K, Arcasoy A, et al. (1989) High risk subgroup of acute myelomonocytic leukemia (AMML) with orbita-ocular granulocytic sarcoma (OOGS) in Turkish children. Retrospective analysis of clinical, hematologucal, ultrastructural and therapeutical findings of thirty-three OOGS. Acta Haematol 81: 80-85.

12. Dusenbery KE, Howells WB, Arthur DC, Alonzo T, Lee JW, et al. (2003) Extramedullary leukemia in children with newly diagnosed acute myeloid leukemia: a report from the Children's cancer group. J Pediatr Hematol Oncol 25: 760-768.

13. Harris AC, Kitko CL, Couriel DR, Braun TM, Choi SW, et al. (2013) Extramedullary relapse of acute myeloid leukemia following allogeneic hematopoietic stem cell transplantation: incidence, risk factors and outcomes. Hematologica 98:179-184.

14. Lee KH, Lee JH, Choi SJ, Lee JH, Kim S, et al. (2003) Bone marrow vs extramedullary relapse of acute leukemia after allogeneic hematopoietic cell transplantation: risk factors and clinical course. Bone Marrow Transplant 32: 835-842.

15. Pileri SA, Ascani S, Cox M, Campidelli C, Bacci F, et al. (2007) Myeloid sarcoma: Clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. Leukemia 21: 340-350.

16. Chevallier P, Mohty M, Lioure B, Michel G, Contentin N, et al. (2008) Allogeneic hematopoietic stem-cell transplantation for myeloid sarcoma: a retrospective study from the SFGM-TC. J Clin Oncol 26: 4940-4943.

17. Vedy D, Muehlematter D, Rausch T, Stalder M, Jotterand M, et al. (2010) Acute myeloid leukemia with myeloid sarcoma and eosinophilia: prolonged remission and molecular response to imatinib. J Clin Oncol 28: 33-35.

18. Piccaluga PP, Martinelli G, Rondoni M, Malagola M, Gaitani S, et al. (2004) Gemtuzumab ozogamicin for relapsed and refractory acute myeloid leukemia and myeloid sarcoma. Leuk Lymphoma 45:1791-1795.

19. Hicsonmez G, Ozsoylu S, Tuncer AM (1991) Differentiation of myeloid leukemic cells induced by high-dose methylprednisolone in patients with acute myeloblastic leukemia and its therapeutic potential. Leuk Res 15: 537-541.

20. Hicsonmez G (2006) 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. Leuk Res 30: 60-68.

21. Hicsonmez G (2010) A novel approach to treatment in childhood acute myeloblastic leukemia and myelodysplastic syndrome with high-dose methylprednisolone as a differentiation- and apoptois-inducing agent of myeloid leukemic cells. Turk J Hematol 27: 1-7.

22. Hicsonmez G, Ozsoylu S, Tuncer AM, Erturk G, Ozbek N, et al. (1991) Direct morphological evidence of high-dose methylprednisolone-induced maturation of leukemic cells in children with acute nonlymphoblastic leukemia. Exp Hematol 19: 232-233.

23. Hicsonmez G, Ozbek N, Kale G, Erdem G, Bilgic S, et al. (1996) Dramatic effect of high-dose methylprednisolone on orbital granulocytic sarcoma. Pediatr Hematol Oncol 13: 187-190.

24. Hicsonmez G, Cetin M, Aslan D, Ozyurek E (2003) The role of short course of high-dose methylprednisolone in children with acute myeloblastic leukemia (FAB M2) presented with myeloid tumor. Pediatr Hematol Oncol 20: 373-379.

25. Hicsonmez G, Cetin M, Yenicesu I, Olcay L, Koc A, et al. (2001) Evaluation of Children with myelodysplastic syndrome: Importance of extramedullary disease as a presenting symptom. Leuk Lymphoma 42: 665-674.

26. Ozyurek E, Alioglu B, Coskun M, Ozbek N (2006) Successful use of short-course high-dose methylprednisolone in a child with acute myeloblastic leukemia (FAB M2) and myeloid tumor. Leuk Lymphoma 47: 923-925.

27. Isik P, Tavil B, Tunc B, Yarali N, Demir A, et al. (2011) Extramedullary orbital granulocytic sarcoma without bone marrow involvement: A report of two cases. Pediatr Hematol Oncol 28: 65-70.

28. Takeda M, Yamaguchi S, Eguchi K, Kajiume T, Nishimura S, et al. (2009) Spinal epidural granulocytic sarcoma in a child precedent to clinical manifestation of acute myeloid lymphoma: case report. Neurol Med Chir (Tokyo) 49: 221-224.

29. Benucci R, Annessi G, Signoretti S, Simoni R (1996) Minimally differentiated acute myeloid leukaemia revealed by specific cutaneous lesions. Br J Dermatol 135: 119-123.

30. Zhou L, Landa C, Zaiden R (2012) An unusual case of disseminated lymphadenopathy. Clin Adv Hematol Oncol 10: 64-66.

31. Kwan LY, Targan SR, Shih DQ (2011) A case of steroid-dependent myeloid granulocytic sarcoma masquerading as Crohn's disease. World J Gastroenterol 17: 2446-2449.

32. Nikolic B, Feigenbaum F, Abbara S, Martuza RL, Schellinger D (2003) CT changes of an intracranial granulocytic sarcoma on short-term follow-up. AJR Am J Roentgenol 180: 78-80.

33. Hiçsönmez G, Cetin M, Tunç B, Tuncer AM, Gümrük F, et al. (1998) Dramatic resolution of pleural effusion in children with chronic myelomonocytic leukemia following short-course high-dose methylprednisolone. Leuk Lymphoma 29: 617-623.

34. Matsushima T, Murakami H, Kim K, Uchiumi H, Murata N, et al. (1995) Steroid-responsive pulmonary disorders associated with myelodysplastic syndromes with der(1q;7p) chromosomal abnormality. Am J Hematol 50: 110-115.

35. Azoulay É, Canet E, Raffoux E, Lengliné E, Lemiale V, et al. (2012) Dexamethasone in patients with acute lung injury from acute monocytic leukaemia. Eur Respir J 39: 648-653.

36. Hicsönmez G, Tuncer AM, Guler E, Tan E, Tekelioglu M (1993) The potential role of high-dose methylprednisolone on the maturation of leukemic cells in children with acute promyelocytic leukemia (APL). Exp Hematol 21: 599-601.

37. Hiçsönmez G, Tuncer M, Toksoy HB, Yenicesu I, Cetin M (1999) Differentiation of leukemic cells induced by short-course high-dose methylprednisolone in children with different subtypes of acute myeloblastic leukemia. Leuk Lymphoma 33: 573-580.

38. Hiçsönmez G, Cetin M, Okur H, Erdemli E, Gürgey A (2003) The potential effect of short-course high-dose steroid on the maturation and apoptosis of leukemic cells in a child with acute megakaryoblastic leukemia. Leuk Lymphoma 44: 1037-1042.

39. Hiçsönmez G, Erdemli E, Tekelioglu M, Tuncer AM, Ozbek N, et al. (1996) Morphologic evidence of apoptosis in childhood acute myeloblastic leukemia treated with high-dose methylprednisolone. Leuk Lymphoma 22: 91-96.

40. Ozbek N, Erdemli E, Hicsonmez G, Okur H, Tekelioglu M (1999) Effects of methylprednisolone on human myeloid leukemic cells in vitro. Am J Hematol 60: 255-259.

41. Suzuki K, Ohishi K, Sekine T, Masuya M, Katayama N (2007) Selective blast cell reduction in elderly patients with acute myeloid leukemia secondary to myelodysplastic syndrome treated with methylprednisolone. Int J Hematol 85: 344-349.

42. Dobos J, Kenessey I, Tímár J, Ladányi A (2011) Glucocorticoid receptor expression and antiproliferative effect of dexamethasone on human melanoma cells. Pathol Oncol Res 17: 729-734.

43. Tan YJ, Teng E, Ting AE (2003) A small inhibitor of the interaction between Bax and Bcl-X(L) can synergize with methylprednisolone to induce apoptosis in Bcl-X(L)-overexpressing breast-cancer cells. J Cancer Res Clin Oncol 129: 437-448.

44. McLean JS, Frame MC, Freshney RI, Vaughan PF, Mackie AE, et al. (1986) Phenotypic modification of human glioma and non-small cell lung carcinoma by glucocorticoids and other agents. Anticancer Res 6: 1101-1106.

45. Xu MJ, Fang GE, Liu YJ, Song LN (2002) Effects of glucocorticoid on proliferation, differentiation, and glucocorticoid receptor expression in human ovarian carcinoma cell line 3AO. Acta Pharmacol Sin 23: 819-823.

46. Kawashima H, Ogose A, Hayami T, Yamagiwa H, Hatano H, et al. (2003) Effect of dexamethasone on growth inhibition and chondrogenic maturation of human chondrosarcoma. J Orthop Sci 8: 341-345.

47. Corsello SM, Roti G, Ross KN, Chow KT, Galinsky I, et al. (2009) Identification of AML1-ETO modulators by chemical genomics. Blood 113: 6193-6205.

48. Joha S, Nugues AL, Hétuin D, Berthon C, Dezitter X, et al. (2012) GILZ inhibits the mTORC2/AKT pathway in BCR-ABL(+) cells. Oncogene 31: 1419-1430.

49. Lotem J, Sachs L (1994) Control of sensitivity to induction of apoptosis in myeloid leukemic cells by differentiation and bcl-2 dependent and independent pathways. Cell Growth Differ 5: 321-327.

50. Kasukabe T, Okabe-Kado J, Hozumi M, Honma Y (1994) Inhibition by interleukin 4 of leukemia inhibitory factor-, interleukin 6-, and dexamethasone-induced differentiation of mouse myeloid leukemia cells: role of c-myc and junB proto-oncogenes. Cancer Res 54: 592-597.

51. Xu ZX, Xu Y, Zhu JK, Li CX, Li Y, et al. (2001) Effects of dexamethasone on Flt3 receptor expression and proliferation induced by recombinant human Flt3 ligand in malignant hematopoietic cells. Acta Pharmacol Sin 22: 534-540.

52. Reikvam H, Olsnes AM, Gjertsen BT, Ersvaer E, Bruserud O (2009) Nuclear factor-kappaB signaling: a contributor in leukemogenesis and a target for pharmacological intervention in human acute myelogenous leukemia. Crit Rev Oncog 15: 1-41.

53. Yuksel S, Saydam G, Uslu R, Sanli UA, Terzioglu E, et al. (2002) Arsenic trioxide and methylprednisolone use different signal transduction pathways in leukemic differentiation. Leuk Res 26: 391-398.

54. Kaymaz BT, Selvi N, Saydam G, Sahin F, Kosova B (2012) Methylprednisolone induces apoptosis by interacting with the JAK/STAT pathway in HL-60 and K-562 leukemic cells. Hematology 17: 93-99.