Leukemia Research Reports 14 (2020) 100220

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Isotretinoin is active in the initial management of acute pro-myelocytic leukemia

Husain Y. Alkhaldy[a,b,*], Ali M. Assiri[c], Sohaila Fatima[a,b], Tarek Owaidah[d]

[a] College of Medicine, King Khalid University, Abha, Saudi Arabia
[b] Aseer Central Hospital, Abha, Saudi Arabia
[c] College of Medicine, Najran University, Najran, Saudi Arabia
[d] Department of pathology and Laboratory medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

ARTICLE INFO

Keywords:
Promyelocytic
Isotretinoin
Leukemia

ABSTRACT

Pro-myelocytic acute leukemia (APL) is characterized by the proliferation of cells blocked at promyelocytic stage and ATRA is the choice of initial treatment because of the APL sensitivity to this compound. In this case study we report a 28-year-old man who presented to the Emergency Department with epistaxis, petechial rash, and fever. Laboratory tests revealed the presence of high white blood cell count with 60% blasts and evidence of coagulopathy. The diagnosis was confirmed later as APL. Because of the delayed transfer to the reference center and unavailability of ATRA initial treatment, the patient received isotretinoin, a related compound. The treatment was successfully implemented in the initial management of acute pro-myelocytic leukemia as patient condition improved. isotretinoin could be used as an alternative therapy for ATRA whenever the latter is not available. further research is needed to establish the appropriate doses and to assess the potential risk of differentiation syndromes.

1. Introduction

Non-ATRA (All trans-retinoic acid) vitamin A derivatives like isotretinoin (13-*cis*-retinoic acid) are used widely for dermatological indications like acne. In this study we report a case where isotretinoin was successfully used in the initial therapeutic management of acute pro-myelocytic leukemia (APL).

2. Case report

A 28-year-old man presented to the Emergency Department of our hospital with a one-week history of low-grade fever, fatigue, and epistaxis. The physical examination revealed ongoing nasal bleeds, scattered petechial rash. Rest of examination was otherwise unremarkable. Analysis of blood parameters showed a white blood cell count (WBC) of 13,000/µl, hemoglobin 9.5 g/dl, and platelet count of 11,000/µl. Peripheral blood smear showed circulating abnormal promyelocytes with bilobed nuclei at 60% without Auer rods (Fig. 1:A-C). Furthermore, fibrinogen plasma level was 1.5 g/l (for a reference range of 1.8–3.5 g/l), prothrombin time (PT) was mildly elevated, 13.7 seconds (International Normalized Ratio (INR): 1.327), and D-dimer was positive. The results of blood tests led to the diagnosis of acute leukemia and patient was further referred to a specialized center.

Pending his acceptance, the patient required platelets transfusion on daily basis to control bleeding. APL was suspected due to the peripheral blood morphology and abnormal coagulation profile. Bone marrow procedure was deferred as patient was planned for immediate referral. Due to unavailability of ATRA, the patient received isotretinoin (Accutane) at dose 30 mg po bid (about 0.6 mg/kg/day) started after 48 h of presentation. After 5 days, the WBC count trended down, and blasts were not further detected (Fig. 2). The platelet count was stabilized then increased without further transfusion. Bone marrow These results suggested that the patient improved after isotretinoin treatment. After referral to a higher-level center, bone marrow was done (Fig. 1:D) and the diagnosis of APL was confirmed by molecular and cytogenetics. The patient was started on ATRA treatment. However, he developed an ATRA differentiation syndrome immediately after the first dose. The patient was treated with ATRA combined with chemotherapy and eventually achieved complete remission.

* Corresponding author at: Department of Internal Medicine, College of Medicine, King Khalid University, Aseer Central Hospital, P.O.BOX 641 Postal Code 61421, Abha, Saudi Arabia.
E-mail address: halkhaldy@kku.edu.sa (H.Y. Alkhaldy).

https://doi.org/10.1016/j.lrr.2020.100220
Received 22 April 2020; Received in revised form 20 July 2020; Accepted 5 August 2020
Available online 07 August 2020

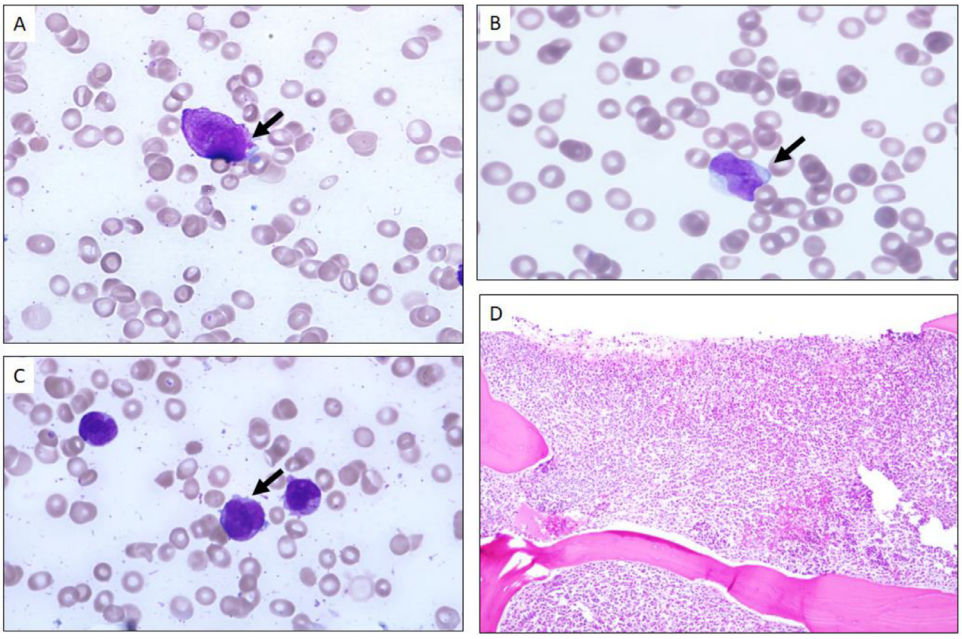

Fig. 1. Light micrographs of studied samples. A and B: peripheral blood smear showing promyelocytes (arrow). C: bone marrow biopsy showing promyelocytes with convoluted nucleus (arrow). D: bone marrow core biopsy showing hypercellular bone marrow with predominance of promyelocytes.

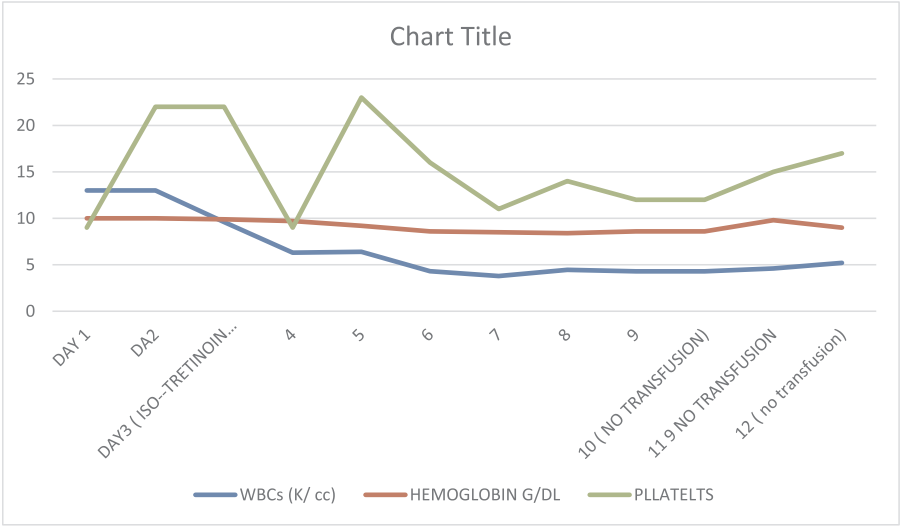

Fig. 2. Blood parameters levels during patient's hospitalization. WBC count was stabilized after treatment with isotretinoin (30 mg po bid).

3. Discussion

APL is characterized by the proliferation of cells blocked at promyelocytic stage [1,2]. The disease presents with coagulation disorders and severe bleeding, which can lead to fatal hemorrhages [3]. Typical symptoms include fatigue, weakness, fever, ecchymosis, epistaxis, and gingival bleeding along with elevated white blood cell count and low platelets count [4]. Underlying genomic translocation leads to expression of a fusion gene named promyelocytic leukemia-retinoic acid receptor-α (PML-RARα), expressed in almost all cases [5,6]. Diagnosis is supported by microscopic examination of peripheral blood and bone marrow smears and genetic testing for PML-RARα. The presences of promyelocytes with Auer rods in peripheral blood smears is highly suggest APL diagnosis.

ATRA is considered the agent of choice for initial management of APL. It induces final maturation of promyelocytes and apoptosis [4]. Because of this, ATRA has had a big impact on the prognosis of APL and in combination with chemotherapy a high remission rate is achieved [7]. Differentiation syndrome, a potentially serious sequel can occur. It may present with renal dysfunction, hepatic dysfunction, respiratory distress, and edema. The WBC count is usually high and dexamethasone administration is needed to control this complication [8]. isotretinoin (13-*cis*-retinoic acid) is a closely related in structure to ATRA. Isotretinoin *in vivo* and *in vitro* activity against APL has been reported before. Flynn et al. [9] reported a response to 13-*cis*-retinoic acid (100 mg/sq. m/day) in a young patient with APL who failed initial chemotherapy. After 13 days of treatment, the peripheral blood and bone marrow showed evidence of maturation. Although the patient died from disseminated candidiasis, no differentiation syndrome was reported. Also, *in vitro* studies confirmed that retinoic acid, a vitamin A derivative, inhibited chemically induced malignant transformation [10] and caused differentiation of HL-60 (human promyelocytic leukemia cell line 60) promyelocytes [11]. Moreover, Vitamin-A-deficient rats developed premalignant epidermal lesions that were reversible after repletion of retinoids which suggested that physiologic compounds may be used as differentiation inducers [12]. We have used isotretinoin for

multiple patients with suspected APL, few of them have the diagnosis later confirmed. However, the duration of use was short and the effect on hematological parameters was not as pronounced as in this patient. None of them however developed any unwanted side effects or liver impairment.

4. Conclusions

This report and the cited literature suggest that isotretinoin might have differentiation effect on malignant promyelocytes. The role of isotretinoin in the treatment of APL needs to be further evaluated. It is still unknown whether the risk of differentiation syndrome is lower or what the appropriate dose is. In circumstances when APL is suspected but ATRA is not available, we believe that isotretinoin could be used as a therapeutic alternative for ATRA until the latter is available . We also advise clinicians to exercise cautions when switching to ATRA upon confirmation of diagnosis as early differentiation syndrome might develop.

References

[1] J.M. Bennett, D. Catovsky, M.T. Daniel, G. Flandrin, D.A. Galton, H.R. Gralnick, et al., Proposed revised criteria for the classification of acute myeloid leukemia. A report of the FrenchAmerican-British Cooperative Group, Ann. Intern. Med. 103 (1985) 620–625 5.

[2] R.M. Stone, R.J. Mayer, The unique aspects of acute promyelocytic leukemia, J. Clin. Oncol. 8 (1990) 1913–1921.

[3] M.S. Tallman, H.C. Kwaan, Reassessing the hemostatic disorder associated with acute promyelocitic leukemia, Blood 79 (1992) 543–553.

[4] Kotiah S.D., Besa E.C. Acute promyelocytic leukemia: practice essentials, background, pathophysiolog[Internet]. 2019 [accessed 3rd December 2019]. Available at:https://emedicine.medscape.com/article/1495306-overview.

[5] A.R. Mistry, E. Wessel Pedersen, E. Solomon, D Grimwade, The molecular pathogenesis of acute promyelocytic leukaemia: implications for the clinical management of the disease, Blood Rev. 17 (2003) 71–97.

[6] A. Melnick, J.D. Licht, Deconstructing a disease: rARα, its fusion partners, and their roles in the pathogenesis of acute promyelocytic leukemia, Blood 93 (1999) 3167–3215.

[7] J. Gregory, J. Feusner, Acute promyelocytic leukaemia in children, Curr. Oncol. Rep. 11 (2009) 439–445.

[8] P. Montesinos, M.A. Sanz, The differentiation syndrome in patients with acute promyelocytic leukemia: experience of the pethema group and review of the literature, Mediterr. J. Hematol. Infect. Dis. 3 (1) (2011) e2011059.

[9] P. Flynn, W. Miller, D. Weisdorf, D. Arthur, R. Brunning, R Branda, Retinoic acid treatment of acute promyelocytic leukemia: *in vitro* and *in vivo* observations, Blood 62 (6) (1983) 1211–1217.

[10] R.L. Merriman, I.S. Bertram, Reversible inhibition by retinoids of 3-methylcholanthrene-induced neoplastic transformation in C3 HI OT'/ clone 8 cells, Cancer Res. 39 (1979) 166 1, I 979.

[11] T.R. Breitman, S.E. Selonick, S.J Collins, Induction of differentiation of the human promyelocytic leukemia cell line (HL-60) by retinoic acid, Proc. Nat. Acad. Sci. USA 77 (1980) 2936.

[12] S.B. Wolbach, P.R. Howe, Tissue changes following deprivation of fat soluble A vitamin, J. Exp. Med. 42 (1925) 753.