Journal of Leukemia
ISSN: 2329-6917

Lin et al., J Leuk 2015, 3:1
DOI: 10.4172/2329-6917.1000168

Letter to the Editor Open Access

12-O-Tetradecanoylphorbol-13-Acetate for Refractory Secondary Acute Myeloid Leukemia

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Rec date: September 4, 2014, **Acc date:** November 24, 2014; **Pub date:** November 30, 2014

Letter to the Editor

In December 2011, a 42-year-old woman was referred to our department. The patient was previously diagnosed with breast cancer in June 2009. She received 6 courses of chemotherapy after having breast tumor resection, and achieved complete remission (CR) after chemotherapy. Then tamoxifen was given for 6 months as a subsequent endocrine therapy. In September 2011, the patient was diagnosed with acute myeloid leukemia-M2 (AML-M2) due to a fever of 39.0. The routine blood test indicated that the white blood count(WBC) was 43.67×10^9/L, absolute neutrophil count (ANC) was 0.8×10^9/L, hemoglobin was 57 g/L, platelets count was 22×10^9/L, and the myeloblasts accounted for 48% in the peripheral blood as well as 79% in the bone marrow. The patient failed to reach CR after a course of DA (daunorubicin+cytarabin) chemotherapy as the myeloblasts still accounted for 68% in bone marrow. However, she was not able to get CR after the HA (homoharringtonine+cytarabin) based regimens due to 63% of myeloblasts in bone marrow.

On admission in December 2011, her blood count showed WBC 26.65×10^9/L, hemoglobin 117 g/L, platelets count as low as 36×109/L, 28.5% myeloblasts in the peripheral blood and 44.5% myeloblasts in the bone marrow. G-band karyotype analysis revealed 46, XY (20). Flow cytometry revealed that the blast cells were positive for CD13, CD33, CD34, MPO and HLA-DC, but were negative for CD2, CD3, CD19, CD41, CD61, CD64, and CD56. After signed the informed consent, the patient received 12-O-tetradecanoylphorbol-13-acetate (TPA) combined with DA (daunorubicin+cytarabin) based regimens for the 3rd chemotherapy. This specific regimens were as follows: daunorubicin 45 mg/m^2/day for 3 days, cytarabin 150 mg/m^2/day for 7 days, continued with TPA at a dose of 4 μg/kg/day given for 4 days when the white blood cell count decreased to a minimum value, then another 4 days treatment was given at the same dose after 4 days interval. Dexamethasone at the dose of 5 mg was given 30 minutes before the application of TPA to prevent allergic reactions. Nonetheless, the patient still appeared symptoms of fever and chill with the highest temperature reached 39.2, no obvious TPA-related toxicities were observed. CD3+ T cells in peripheral blood were increased significantly after the application of TPA, though they were also detected by flowcytometry before TPA application (Figure 1). The WBC recovered gradually 7 days later after TPA administration, and reached to the normal level after 10 days. The PLT increased 8 days after the treatment and normalized after 12 days. The myeloblasts were reduced to 0.5% in the peripheral blood while 2.0% in the bone marrow when the bone marrow biopsy was taken 14 days after the treatment. This patient received the sibling HLA matched hematopoietic stem cell transplantation after 4 courses chemotherapy of high-dose cytarabin for consolidation therapy.

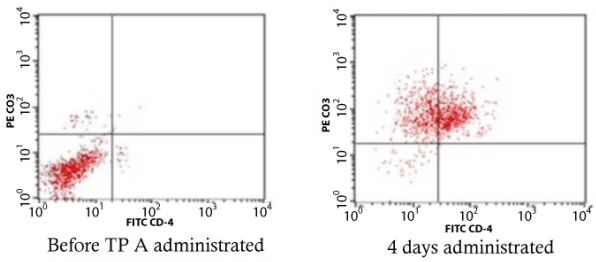

Figure 1: CD3+T cells in the peripheral blood were increased rapidly after TPA administrated compared with the previously detected by the flow cytometry. CD3+ and CD4+ T cells were accounted for 7.6% and 3.5%, respectively, before the TPA was applied, but increased significantly after 4 days treatment of TPA, which were accounted for 92%% and 57.1%, respectively.

It is not rare that the occurrence of AML as a secondary malignancy follows the primary solid cancer especially breast cancer. This is associated with the chemotherapy and radiotherapy the patients previously received at the risk of subsequent AML, although the absolute risk remained unknown [1-3]. There is still not a particularly effective treatment for the secondary AML. For this poor prognosis group of patients, allogeneic hematopoietic stem cell transplant (Allo-HSCT) likely represents the only curative option [4]. However, to achieve a complete remission after chemotherapy forms a prerequisite for a successful transplantation [5], therefore, to explore new treatment strategies becomes an urgent task at present. It was shown that TPA could induce apoptosis in some carcinoma cell lines include leukemia cell line, such as skin epidermal JB6 cells, gastric cancer cells, prostate cancer cells and leukemia cells [6-8]. As it has been demonstrated that TPA induces apoptosis in some leukemia cells, investigators in China administered TPA to patients with myeloid malignancies, with a variety of doses and schedules considered. It prompted the initiation of a Phase I clinical trial of TPA as a single agent for patients with re-lapsed/refractory malignancies at the cancer institute of New Jersey. These studies confirmed the feasibility of TPA administration to humans as a therapy for patients with a variety of malignant and nonmalignant disorders [9]. In our study, it indicated that the patient achieved CR through the chemotherapy of TPA combined with DA based regimens; CD3 and CD4 expressed T cells in peripheral blood were increased significantly after administration of TPA; the myeloblasts were decreased obviously probably because of the significantly increased CD4+ T cells induced by TPA which promoted the effect of DA chemotherapy [10]. However, the mechanism of immunophenotypic response to TPA is still unclear.

The major adverse effect on this patient was transient fever and chill occurred 1 h after the completion of the infusion. Therefore, TPA seems to represent a reasonable salvage treatment in refractory AML. Because of the unclear mechanism on leukemia cells, more studies about primary leukemia cells exposed to TPA are needed.

Acknowledgments

The authors would like to thank the patient for her cooperation. This work has been supported by the grants from the National Natural Science Foundation of China (grant nos.: 30900637).

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