

THROMBOSIS IN ACUTE PROMYELOCYTIC LEUKEMIA PATIENTS TREATED BY ALL-TRANS RETINOIC ACID (ATRA) – A PROSPECTIVE RESEARCH THROMBOSIS INDUCED BY ATRA TREATMENT

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Summary. Acute promyelocytic leukemia (APL) is characterized by clone proliferation and accumulation of promyelocytes with characteristic morphology, fibrinolysis, proteolysis and disseminated intravascular coagulation. It is accepted that all-trans retinoic acid (ATRA) alone or combined with cytostatics, has to be used in the first swing of APL, in APL resistant to cytostatics and in relapse of APL treated by cytostatics. Though usually well tolerated, ATRA can induce side effects known as ATRA syndrome. Deep vein thrombosis is a rare complication of ATRA treatment. In a four years long prospective research, we determined the incidence and the risk of thrombosis in APL patients treated by ATRA. The study involved 12 APL patients of both gender, with median age of 47.8 years. All patients received 110995 mg of ATRA in total, 9246.25 mg per person IN average. A deep vein thrombosis developed in one patient (8.3 %) after receiving ATRA cumulative dose of 2700 mg. The drug was immediately withdrawn and was reintroduced when thrombosis disappeared. Thrombosis was probably the consequence of transitory hypercoagulability caused by the drug. In further three years of ATRA treatment, thrombosis did not reappear. The patient is still in remission. Careful observation of each APL patient treated by ATRA is necessary, as well as the early diagnosis and adequate treatment of ATRA-caused thrombosis.

Key words: Acute promyelocytic leukemia, ATRA (all-trans retinoic acid), ATRA syndrome, thrombosis

Introduction

Acute promyelocytic leukemia (APL) presents as acute myeloid leukemia that is classified as AML-M3 type according to French-American-British (FAB) co-operative group. It is characterized by clone proliferation and accumulation of promyelocytes with characteristic morphology, fibrinolysis, proteolysis, and disseminated intravascular coagulation (DIC) (1-5). Basically, is a chromosome disorder manifested by translocation t (15;17), which presents chromosome marker of APL. Hybrid PML/RAR α gene most important in the pathogenesis of APL is created from PML (promyelocytic leukemia) gene located at chromosome 15 and retinoic acid receptor alpha (RAR α) gene located at chromosome 17 (6-8).

Until recently, intensive chemotherapy of APL was usually presented by combination of anthracyclins and cytarabine (cytosine arabinoside, ARA - C). At the same time, it was the only effective treatment of APL. Findings of Chinese hematologists that in patients with newly diagnosed APL, as well as in relapse of the disease, high level (96%) of complete remission (CR) is accomplished by the application of tretinoin (all-trans retinoic acid, ATRA), changed the therapy approach, increased the understanding of APL biology and opened

new perspectives in leukemia treatment (9-11). Today, ATRA alone, or combined with cytostatics, is accepted as induction treatment of APL (12-16), in cytostatics resistant APL and in relapse of APL with combinations of cytostatic (3, 17-19). In the cases of early APL relapse within 3-4 months after the ATRA therapy, response to the ATRA cannot be expected in the future, in spite of the applied high dosages of ATRA. Patients with late-onset relapse within 4-25 months can achieve remission after repeated application of ATRA (3,6).

Applied in pharmacological dosages, ATRA influences RAR α gene activity. Degradation of PML/RAR α gene is registered during the ATRA treatment, as well as returning of PML gene into the nuclear corpuscles. It presents the cause or the consequence of promyelocyte differentiation. It induces terminal differentiation of malignant promyelocytes.

The advantages of ATRA treatment in comparison to other drugs are manifested in a faster normalization of the coagulation disturbances (4, 20-22).

The therapy with ATRA lasts for 30-90 days. Complete remission is usually achieved within this period (7).

At the Clinic of Hematology in Nis, until 2002, patients with less than 5×10^9 /L of WBC were treated by ATRA only, with the addition of supportive therapy. If the WBC was above 5×10^9 /L, ATRA was combined

with other drugs, usually with DNR (applied during three consecutive days) and ARA-C (during seven consecutive days). Standard treatment for consolidation of the disease started after complete remission.

Since 2002, PETHEMA/LPA 99 protocol was introduced for APL PML/RARA positive patients. Induction therapy contained ATRA applied together with idarubicin (AIDA).

Although ATRA is usually well tolerated, it can demonstrate a number of side effects designated as ATRA syndrome (19, 23-25).

The deep vein thrombosis as a complication of ATRA application is rare. Until now, single cases of thromboembolic complications were reported during the application of ATRA, and some of them with fatal outcome (26). But, there are no data about ATRA risk/benefit ratio and the frequency of ATRA-evoked thrombosis, calculated on the basis of ATRA utilization is not prospectively investigated. Thus, the aim of our research was to determine the incidence and outcome of this complication in APL patients treated by PETHEMA/LPA 99 protocol, as well as the exposition of patients to ATRA.

Materials and Methods

This research was prospective. It was performed at the University Clinic of Hematology in Nis. The research started in January 2002 and was finished in December 2006. Only newly diagnosed APL patients were followed.

The diagnosis of APL was made on the basis of hematological, biochemical and cytogenetic examinations of peripheral blood and bone marrow aspirate. The finding of translocation t (15;17) was the diagnostic criteria. A cytogenetic analysis of karyotype was performed by a fast, modified Giemsa band method (6).

Patients were treated by PETHEMA/LPA 99 protocol (27).

Induction therapy consisted of idarubicin (IDA) 12 mg/m² on days 2, 4, 6 and 8 (patients aged over 70, only on days 2, 4, 6) and of ATRA 45 mg/m²/day until CR.

Patients who achieved CR and hematological recovery (neutrophils higher than 1,5 x 10⁹ /L and platelets higher than 100 x 10⁹ /L) were treated by three successive courses of consolidation therapy in a monthly schedule, by LPA 96 or by LPA 96 + ATRA protocol (27).

LPA 96 protocol without ATRA was applied in six patients with a leukocyte count lower than 10 x 10⁹ /L, and a platelet count higher than 40 x 10⁹ /L (low risk patients).

LPA96 protocol with ATRA was applied in six patients, these with a leukocyte and a platelet count lower than 10 x 10⁹ /L and 40 x 10⁹ /L, respectively, and with a leukocyte count higher than 10 x 10⁹ /L (intermediate or high risk patients). It consisted of three consolidation courses.

The first consolidation course included IDA, 7 mg/m² /day by intravenous infusion on days 1, 2, 3, 4, and

ATRA, 45 mg/m² /day orally, divided into two doses, given from days 1 to 14.

The second consolidation course: mitoxantrone, 10 mg/m² /day by intravenous infusion on days 1, 2, 3, 4, 5 and ATRA, 45 mg/m² /day orally, divided into two doses, applied on days 1 to 14.

The third consolidation course: IDA, 12 mg/m² /day by intravenous infusion on days 1 and 2, and ATRA, 45 mg/m² /day orally, divided into two doses, on days 1 to 14.

Post consolidation/maintenance treatment in all APL patients consisted of 6-mercaptopurine in a dose of 50 mg/m² /day orally, applied one month after final consolidation; methotrexate, 15 mg/m² /weekly, intramuscularly, one month after the final consolidation and ATRA 45 mg/m² /day orally, for 15 days every three months, until a two-year period is completed. Methotrexate and 6-mercaptopurine are discontinued in the days of ATRA treatment.

The safety of ATRA was monitored during the research period in the light of deep vein thrombosis in APL patients treated by PETHEMA/LPA 99 protocol. The diagnosis of thrombosis was performed on the clinical manifestation, biochemical parameters and ultrasound examination of blood vessels.

Utilization of ATRA was calculated on the total amount of ATRA that each patient received. It was the basis for determining the drug amount that could eventually cause thrombosis.

The Naranjo scoring methods was used to specify the caused links between symptoms/signs and ATRA (28).

Results and Discussion

There were 12 newly diagnosed APL patients (six male, six female), average age 47.8 (range 38-60 years). In all of them, the remission occurred on average within 30-55 days after the initiation of the therapy (PETHEMA/LPA 99 protocol).

During the study period, patients received the total of 110955 mg of ATRA. In average, 9246.25 mg of ATRA (2240-12870 mg) was administered to each patient. Thrombosis was registered only once, in a 44-old patient. He was hospitalised for the first time at Clinic of Hematology in Nis in November, 2002. He denied significant illnesses in personal and family history, as well as drugs allergy. Physical examination was normal.

Biochemical parameters, like urinalysis, serum electrolytes, serum creatinine, serum protein and liver function tests were in the referent ranges. Coagulation abnormalities were not present. Ultrasound examination of abdomen was without pathological findings.

On day 16 after the initiation of ATRA therapy, the patient reported muscle pain in both legs. Since coagulation factors and D-dimer were within the referent values, it was concluded that myalgia probably developed as a consequence of ATRA, the side effect described in literature (14, 29, 30). Because of that, ATRA was discontinued and corticosteroid therapy was started (dexa-

methasone, 10 mg intravenously every 12 hours) (31). Pain subsided after three days of corticosteroid treatment. ATRA was introduced on day 21.

The patient reported severe pain in left lower leg on day 27. Oedema and erythema of left calf were found, together with dilated veins. Pulses of a. dorsalis pedis and a. tibialis were preserved. Dilatation of v. popliteae of left leg below the place of total occlusion was found on blood vessels ultrasound examination.

Antithrombin III, protein C and S were in referent values. Except slightly increased values of D-dimer of 0.5 mg/L, (reference value 0.3 mg/L), were adequate to the other results, like prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen level, as well as lupus anticoagulans.

According to the above findings, thrombophilia was excluded and a diagnosis of v. popliteae thrombosis was made.

Taking into consideration all potential factors that could cause thrombosis, the suspected was ATRA. Thrombosis development is possible during ATRA treatment, which is a side effect of this drug. Thus, we applied Naranjo scoring method to estimate relation between thrombosis registered in our patient and ATRA. According to this method, it was concluded that thrombosis probably was induced by ATRA. It appeared after the cumulative dose of 2700 mg of ATRA.

Because of that, application of ATRA was aborted immediately and anticoagulant treatment was introduced (fraxiparin for seven days in a dose of 0.3 ml - 3000 IU every 12 hours given intravenously, while oral anticoagulants were applied afterwards).

Two-months of anticoagulant therapy resulted in the thrombosis resolution, since the D-dimer was in referent values, and v. popliteae was free of thrombotic masses, documented by left leg blood vessels ultrasound examination. Thereafter, the ATRA application was continued. Thrombosis did not reappear in spite of constant three-year-long ATRA treatment. Until the last control performed in December 2006, the patient was still in complete remission.

Appearance of ATRA syndrome is a serious complication of ATRA treatment. Latent period of ATRA syndrome is 2-47 days from the beginning of drug administration (7).

Some adverse effects of ATRA are registered in 20-25% APL patients. This syndrome includes abundant clinical features, such as fluid retention (edema and increase in body weight), increased body temperature, muscle and bone pain. Progressive respiratory distress syndrome can develop later, as well as skin infiltrates, pleural and pericardial effusion, and hypotension. These could be followed by increased leukocyte counts, but that is not always the case. The drug (ATRA) has to be temporarily discontinued in ATRA syndrome. Disturbances are thereafter usually reversible, spontaneously or under the appropriate medical treatment (8, 31-33).

ATRA syndrome is most likely the consequence of secretion of cytokines (IL-1, IL-2, IL-6, TNF and IL-8)

by the cells of the immunological system (32). They are responsible for activation and adherence of leucocytes, followed by infiltration of organs with leukemia cells (34, 35).

Thrombosis can also be the isolated ATRA adverse effect (24, 34-36). Pathogenesis of thrombosis in ATRA treated APL patients has not been completely clarified, since ATRA demonstrates both procoagulant and fibrinolytic activities. Besides, thrombosis can be a part of DIC, a clinical manifestation of APL.

Chemotherapy and ATRA in treating APL, described in certain European studies, pointed out significant coagulopathies, which occur within six days of standard chemotherapy (ARA-C and anthracycline), and three days of ATRA treatment (28). In APL patients treated by ATRA only, a primary fibrinolysis disappears within five days of the treatment, while DIC and leukocyte-mediated proteolysis persists during 2-3 weeks of therapy. Although very rare, the last mechanism can lead to transitory hypercoagulability, with increased risk of thrombotic complications (38).

Vasoactive cytokines released from leukaemia cells, differentiated during ATRA treatment, also take a significant role in the pathogenesis of thrombosis, as well as the disturbances of endothelial homeostasis developed during ATRA treatment.

The data of World Health Organization (WHO) on vein thrombosis obtained by spontaneous reports, from the time tretinoin was put in the world market in 1973 until October 2004, contain one vein and three arterial thromboses (39). Beside the presented case, single cases of thrombosis and thromboembolic events were registered in the Medline database (40). In one study, out of 30 APL patients treated by ATRA, thromboembolic complications were registered in five of them. They had deep vein thrombosis and pulmonary embolism (35, 41). Other authors also registered thrombosis induced by ATRA (4, 19, 37, 42). In the organs with developed thrombosis, infarctions were found, too (19, 21, 33, 36, 38).

In our prospective study that lasted for four years, the deep vein thrombosis developed once in a single patient under ATRA treatment. Thrombophilia was excluded as the cause of thrombosis by clinical and laboratory examinations. Most probably, ATRA was a major cause of thrombosis, based on time of onset of thrombotic event and the moment of using ATRA. Thus, it is suggested that thrombosis could be the result of other prothrombotic factors disturbed by ATRA, predominantly these in endothelial cells. Hemostasis of endothelium can be affected by ATRA-induced secretion of endothelial inflammatory and angiogenic cytokines, which can lead to activation of endothelial prothrombotic and proadhesive functions.

The frequency of thrombosis caused by any drug, including ATRA, as well as the risk of drug to induce such reactions, cannot be determined on the single reported case. For these purposes it is essential to find out the total drug utilization, that displays exposure of the patient to the investigated drug. These kinds of re-

searches are widely performed throughout the world and represent the basis for evaluating the frequency of adverse drug events (36).

The appearance of thrombosis, as one of the possible complications of ATRA treated APL patients, was monitored in our research. Twelve patients received 110955 mg of ATRA. After the cumulative dose of 2700 mg, the deep vein thrombosis appeared in one patient (8.3% of patients), probably as the consequence of transitory hypercoagulability caused by the disturbance of endothelial hemostasis. It did not occur along with an average or high, but rather along with a low cumulative dose of ATRA, which coordinates with characteristic latent time of ATRA syndrome development.

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TROMBOZA KOD PACIJENATA SA AKUTNOM PROMIJELOCITNOM LEUKEMIJOM TRETIRANIH ALL - TRANS RETINOIČNOM KISELINOM (ATRA) - PROSPEKTIVNO ISPITIVANJE

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Kratak sadržaj: Akutna promijelocitna leukemija (APL) se karakteriše klonalnom proliferacijom i akumulacijom promijelocita karakteristične morfologije, fibrinolizom, proteolizom i diseminovanom intravaskulnom koagulacijom. Opšte je prihvaćeno da se all-trans retinoična kiselina (ATRA), sama ili u kombinaciji sa citostaticima, koristi u indukciji lečenja APL-a, u APL rezistentnom na citostatike i u relapsu APL-a tretiranom citostaticima. Iako se dobro toleriše, ATRA može izazvati neke neželjene efekte, poznate kao ATRA sindrom. Duboka venska tromboza je retka komplikacija lečenja ATRA-om. Za četiri godine dugog prospektivnog istraživanja, utvrdili smo incidencu i rizik od tromboza kod APL bolesnika tretiranih ATRA-om. Studija je uključivala 12 APL bolesnika, oba pola, prosečnog uzrasta 48,7g. Svi pacijenti, primili su, 110995mg ATRA-e ukupno, 9246,25mg po osobi u proseku. Duboka venska tromboza razvila se kod jednog pacijenta (8,3%) posle primanja kumulativne doze od 2700mg ATRA-e. Lek je momentalno obustavljen i po izlečenju duboke venske tromboze ponovo uključen. Tromboza je verovatno izazvana tranzitornom hiperkoagulabilnošću krvi izazvane lekom. U sledeće tri godine ATRA tretmana, tromboza se više nije pojavljivala. Pacijent je još uvek u remisiji, iako je u poslednjih 12 meseci bez APL terapije. Neophodna je pažljiva opservacija svakog pacijenta tretiranog ATRA-om, kao i rana dijagnoza i adekvatno lečenje ATRA-om izazvane tromboze.

Ključne reči: akutna promijelocitna leukemija, ATRA (all-trans retinoična kiselina), ATRA sindrom, tromboza