THP-ADM in the Treatment of Acute Promyelocytic Leukemia

YOSHIRO UZUKA and YOSHIKO SAITO

Third Department of Internal Medicine, Tohoku University
School of Medicine, Sendai 980

UZUKA, Y. and SAITO, Y. THP-ADM in the Treatment of Acute Promyelocytic Leukemia. Tohoku J. exp. Med., 1985, 146 (1), 1-8 — Three patients, diagnosed as acute promyelocytic leukemia and disseminated intravascular coagulation (DIC), were treated with THP-ADM in combination with heparin and intensive platelet transfusion. Two of the three patients achieved complete remission. The remaining one patient also responded favorably to the therapy and achieved marrow aplasia, and significant improvement of coagulopathy was observed after chemotherapy. However, he suddenly died of intractable congestive cardiac disturbance ten days after the completion of THP-ADM induction therapy. The mechanism of this unique delayed anthracycline-associated cardiotoxicity was discussed. —— acute promyelocytic leukemia (APL); disseminated intravascular coagulation (DIC); THP-ADM; heparin therapy

Acute promyelocytic leukemia (APL) is a unique form of acute leukemia with a high incidence of disseminated intravascular coagulation (DIC) (Hillestad 1957; Gralnick et al. 1972; Bernard et al. 1973; Gralnick and Sultan 1975; Collins et al. 1978) and is characterized by the presence of abnormal promyelocytes whose cytoplasm is packed with coarse granules and which have prominent Auer-like crystalline inclusions and by poor response to chemotherapy. Cytogenetically, a specific chromosome abnormality [t(15q+, 17q−)] (Goldman 1974; Golomb et al. 1976) has been identified in patients with APL.

The therapy of APL must front on two important problems; 1) the aggressive chemotherapeutic eradication of leukemic cells and 2) the control of hemorrhagic disorder.

In 1973 Bernard et al. reported a rate of forty-three percent of complete remission by the treatment of APL with a single agent, daunorubicin (DNR). The effectiveness of this treatment is perhaps due to the rapid antileukemic effect and rapid induction of bone marrow aplasia. With the introduction of DNR, the outcome for patients with APL has greatly improved.

For the management of coagulation disorder the use of heparin was advocated and this has largely become a standard practice (Baker et al. 1964; Gralnick et al.

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In the present study, we evaluated the use of a new anthracycline, THP-ADM (4-o-tetrahydropyranyl adriamycin), developed by Umezawa et al. (1979), in the treatment of APL. Moreover, we studied the effect of low dose heparin administration on the coagulopathy.

**Materials and Methods**

**Patients**

In all three patients the diagnosis of APL was established by bone marrow and peripheral blood examinations. All patients were males, aged forty-six, thirty-five and twenty-one.

**Coagulation studies**

Blood samples were collected into trisodium citrate (9 volumes blood into 1 volume citrate). The studies included hepaplastin test (HT), thrombotest (TT), one-stage prothrombin time (PT) using simplastin (General Diagnostics Co.), Kaolin activated partial thromboplastin time (K-PTT), serial thrombin time (STT), and assay for fibrinogen, fibrinogen and fibrin degradation products (FDP), and antithrombin III activity.

For remission induction THP-ADM in a dose of 20 mg/body was administered daily for three to five days. When a second course of induction was necessary, usually the same or a smaller dose of the drugs was administered.

Each patient was started on a prophylactic infusion of heparin at a dose of fifty to sixty units/kg every six hours. Heparin therapy was discontinued when bleeding was stopped and coagulation data returned to normal. Platelet transfusion using Haemonetics M-30 was performed to maintain the platelet count over than 30,000 to 50,000/mm³.

**Results**

**Cell morphology**

Leukemic cells in Patients 2 and 3 had typical features of hypergranular APL, while those in Patient 1 showed a microgranular variant of hypergranular APL. The correct diagnosis of APL was usually established by cytochemical examination of leukemic cells. Cytochemical analysis showed that the leukemic cells were strongly positive for peroxidase (POX) and AS-D chloroacetate esterase.

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<th>Case</th>
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POX, peroxidase; AS-D CE, AS-D chloroacetate esterase; ANE, alpha-naphthyl acetate esterase.

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1972; Drapkin et al. 1978; Citarrela et al. 1979; Gamba et al. 1979; Sandler et al. 1983).
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(AS-D CE), but negative for alpha-naphthyl acetate esterase (ANE). The leukemic cells had the following phenotypes: Ia—, Fcγ+, Fcγ+, CR— (Table 1).

Coagulation studies

The diagnosis of DIC was considered possible if the patient met one or more of the following criteria (Drapkin et al. 1978); 1) FDP > 20 µg/ml, 2) fibrinogen < 150 mg/100 ml, 3) prolonged prothrombin time > 3 sec above control, and 4) prolonged thrombin time > 3 sec above control. Patients 1 and 3 showed pretreatment abnormalities of coagulation tests suggesting DIC. Patient 2 had normal pretreatment coagulation studies, but developed coagulation abnormalities immediately after the initiation of the chemotherapy.

Fig. 1. Changes of hematological findings and coagulation tests during chemotherapy in Case 1.
Figs. 1 to 3 show the details of the therapy and clinical courses of the three patients. Patient 1 was diagnosed as having APL with DIC and was immediately commenced on chemotherapy using daunomycin, cytosine arabinoside, 6-mercaptopurine and prednisolone (DCMP) (Uzuka 1980). In addition, to control the coagulopathy a bolus injection of heparin at an initial loading dose of fifty U/kg was given every six hours. In this patient, the marrow was interpreted as persistent leukemia after one course of DCMP therapy then the second induction course with THP-ADM was given immediately. After four weeks from the initiation of the second induction course, he achieved complete remission.

Patient 2 achieved complete remission following three courses of induction therapy with THP-ADM. Patient 3 was also treated with THP-ADM in combination with heparin for DIC. He was also well responsive to the treatment and a marked decrease of marrow leukemic cells and improvement of the coagulopathy were observed after chemotherapy, but ten days after the completion of five day course
of THP-ADM induction therapy he suddenly died of intractable congestive cardiac failure.

All three patients presented with varying degrees of bleeding. Within two to five days after chemotherapy was initiated bleeding accelerated and coagulation abnormalities increased in all three patients despite heparinization. However, these returned to normal within six to ten days. Resolution of clinical bleeding antedated or occurred in parallel with these changes.

DISCUSSION

THP-ADM, 4-o-tetrahydropyranyl adriamycin, was synthesized by Umezawa et al. (1979), who found that it was superior to adriamycin in its activity against L1210, and less cardiotoxic than adriamycin in animal experiments.

APL is a unique type of acute leukemia and deserve special consideration for its fulminant course, proneness to DIC, and peculiar morphology (Sultan et al.
1973). A somewhat different therapeutic approach is required in order that the patients may survive the hemorrhagic complication at the initial period of remission induction therapy. Clearly the introduction of anthracycline agents has led to a significant improvement in the treatment of APL where rapid induction of bone marrow aplasia is of great importance. Bernard et al. (1973) reported an eleven percent complete remission (CR) rate before 1967 prior to the availability of daunorubicin, and a forty-three percent CR rate with daunorubicin alone between the years 1967 and 1973. Since 1973 they have continued to use daunorubicin with intensive platelet transfusion and heparin, and recently reported a CR rate of seventy-eight percent in APL (Bernard et al. 1977) Chang et al. (1977) also reported a CR rate of sixty percent in APL, and Daly et al. (1980) reported a CR rate of seventy-five percent in fifteen patients with APL. Other reports on the effect of chemotherapy of APL using daunorubicin alone or in combination with cytosine arabinoside showed CR rates of thirty to sixty-five percent (Groopman and Ellman 1979; Bennet and Boggs 1981).

Our preliminary studies on the effect of chemotherapy in APL showed that substitution of THP-ADM for DNR was promising and should be a part of future chemotherapy program.

Our results favor the cautious use of heparin in conjunction with intensive platelet transfusion prior to initiation of chemotherapy. The clinical course of Patient 3 reported here appeared to be unique. He responded favorably to THP-ADM therapy but he suddenly died of intractable cardiac failure ten days after the completion of five day course of THP-ADM induction therapy.

Cardiac toxicity is a well-recognized dose-related complication of prolonged anthracycline therapy. Less well appreciated is acute lethal cardiac toxicity. These acute cardiac disturbances have usually been observed within twenty-four hours of anthracycline administration (Lantz et al. 1979). The clinical course of the patient was alike a patient reported by Gan et al. (1983). She was a sixteen-year-old schoolgirl presented with APL and ten days after induction therapy with doxorubicin and cytosine arabinoside together with heparinization for the accompanying DIC, she developed near lethal ventricular fibrillation. Gan et al. (1983) described that the exact mechanism for this delayed doxorubicin-associated cardiac toxicity was not clear, but electrolyte disturbance and heparin-doxorubicin interaction might have played a contributory role. Whatever the mechanisms these results suggest that exceptional electrolyte care and judicious timing of heparin and anthracycline therapy are imperative in patients treated with these agents.

References


21) Umezawa, H., Takahashi, Y., Kinishita, M., Naganawa, H., Masuda, T., Ishizuka, M.,