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Abstract

Relapses in nine patients with acute myelocytic leukemia were treated with a combination of aclarubicin (ACR) and cytosine arabinoside (ara-C). ACR, 40 mg/m²/day, was administered daily by intravenous injection from day 1 to day 3 and ara-C, 60-80 mg/m²/day, divided into 2 doses, was given every 12 h by intravenous infusion from day 1 to day 7. Depending on the state of the bone marrow, ACR-ara-C regimen was modified in administration period and repeated after the resting periods of at least 7 days. Complete remission was obtained in 7 of 9 patients (77.8%). The time required for achieving the complete remission varied from 20 to 55 days with a median of 39 days. The duration of complete remission was from 8 to 52 weeks with a median of 22 weeks. Side effects on digestive system such as nausea, vomiting and anorexia, were seen in all patients, although they were managed by symptomatic treatment. The results indicate the effectiveness of this ACR-ara-C regimen in the clinical management of acute nonlymphocytic leukemia.

KEYWORDS: aclarubicin, cytosine arabinoside, chemotherapy, acute myelocytic leukemia

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— BRIEF NOTE —

**TREATMENT OF RELAPSED ACUTE MYELOCYTIC
LEUKEMIA WITH A COMBINATION OF ACLARUBICIN
AND CYTOSINE ARABINOSIDE**

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Abstract. Relapses in nine patients with acute myelocytic leukemia were treated with a combination of aclarubicin (ACR) and cytosine arabinoside (ara-C). ACR, 40 mg/m²/day, was administered daily by intravenous injection from day 1 to day 3 and ara-C, 60-80 mg/m²/day, divided into 2 doses, was given every 12 h by intravenous infusion from day 1 to day 7. Depending on the state of the bone marrow, ACR-ara-C regimen was modified in administration period and repeated after the resting periods of at least 7 days. Complete remission was obtained in 7 of 9 patients (77.8%). The time required for achieving the complete remission varied from 20 to 55 days with a median of 39 days. The duration of complete remission was from 8 to 52 weeks with a median of 22 weeks. Side effects on digestive system such as nausea, vomiting and anorexia, were seen in all patients, although they were managed by symptomatic treatment. The results indicate the effectiveness of this ACR-ara-C regimen in the clinical management of acute nonlymphocytic leukemia.

Key words: aclarubicin, cytosine arabinoside, chemotherapy, acute myelocytic leukemia.

Aclarubicin (ACR) is a new anthracycline antibiotic isolated from the culture of streptomyces galilaeus MA 144-MI by Umezawa *et al.* in Japan (1). ACR binds to DNA and disturbs the template activity for DNA and RNA polymerase (2, 3). The antitumor activity of ACR against leukemia L 1210 and P 388 is similar to daunorubicin (DNR), but slightly less than adriamycin (ADM) (4). ACR is also effective against rat hepatoma AH 41 C (5). A preclinical study showed that the acute cardiotoxicity of ACR in hamsters was less than 1/10 that

of ADM (4). Previous work from our clinic evaluated the clinical effect of this agent on acute myelocytic leukemia (AML) (6).

The present study was designed to evaluate the usefulness of ACR in the treatment of acute nonlymphocytic leukemia in combination with cytosine arabinoside (ara-C).

Materials and methods. Nine patients with AML who had previously been treated with DCMP (DNR, ara-C, 6 mercaptopurine, prednisolone) and/or NCMP (neocarzinostatin, ara-C, 6 mercaptopurine, prednisolone) regimens during the first remission induction and maintenance therapy were entered into this study. The male to female ratio was 5 : 4 and the ages varied from 23 to 51 years old. The therapeutic schedules were as follows: ACR, 40 mg/m²/day, was administered daily intravenous injection from day 1 to day 3 and ara-C, 60 – 80 mg/m²/day, divided into 2 doses, was given every 12 h by intravenous infusion from day 1 to day 7. Depending on the state of the bone marrow, the ACR-ara-C regimen was modified with respect to the administration period and repeated after a resting period at least 7 days.

Patients who achieved complete remission received the same drug combination. ACR, 40 mg/m²/day, was administered by intravenous injection on day 1 and day 3 and ara-C, 60 – 80 mg/m²/day, divided into 2 doses, was given every 12 h s.c. from day 1 to day 4. The maintenance therapy comprised a 4-drug combination of ACR, ara-C or behenoyl ara-C, vincristine and prednisolone.

Responses to the chemotherapy were evaluated by the criteria of Kimura (7). A complete remission was defined as the condition when the bone marrow contained less than 5% blasts and normal levels of erythroid and granuloid series with normal levels of white blood cell and platelet counts.

Results and discussion. Complete remission was obtained in 7 of 9 patients (77.8%). The time needed to obtain complete remission ranged from 20 to 55 days (median: 39 days) and the total dose of antileukemic agent used varied from 180 to 420 mg (median: 330 mg) for ACR and from 400 to 1,560 mg (median: 1,100 mg) for ara-C. The duration of complete remission varied from 8 to 52 weeks (median: 22 weeks) and survivals were from 24+ to 260 weeks (median: 96+ weeks) from time that AML was diagnosed clinically.

Hematological changes during the first reinduction therapy were as follows: the nadir of white blood cell counts was from 160 to 6,100/cmm with a median of 400/cmm. The median of the nadir was 13,000/cmm for the platelet counts and 6,500/cmm for the bone marrow nucleated cells (NCC). The time to the nadir was from 11 to 18 days (median: 15 days) for the white blood cell count, from 15 to 18 days (median: 14 days) for the platelet count and from 9 to 18 days (median: 13 days) for the NCC count.

Toxic manifestations related to the ACR-ara-C regimen are listed in Table 1. Untoward effects on the digestive system such as nausea, vomiting and anorexia

TABLE 1. COMPLICATIONS OF ACR-ARA-C REGIMEN

Anorexia	9/9 cases
Nausea and vomiting	9/9
Loss of hair	0/9
Elevation of serum GOT and GPT	0/9
Episodes of infection	
Pharyngitis	1/9
Tonsillitis	1/9
Pneumonia	2/9
Unknown	4/9
Episodes of bleeding	
Gastrointestinal	0/9
Intracranial	0/9

were seen in all cases, but could be managed by symptomatic treatment. Electrocardiographic studies showed no significant changes before and after chemotherapy. Episodes of infection, which could be controlled by antimicrobial chemotherapy, were recognized in 8 of 9 patients (2 cases with infection of the upper respiratory tract, 2 cases of acute pneumonia and 4 cases of unknown focus).

Progress in the clinical management of acute leukemia such as the development of new antitumor agents and supportive therapy has made complete remission and prolonged survival, however, relapse from such remissions is inevitable. Therefore, optimal schedules for treatment of a relapse have been designed in consideration of the resistance of leukemic cells to antitumor agents and toxic effects as the drugs used accumulate.

DNR was shown to be a useful chemotherapeutic agent available for the treatment of acute leukemia; however, the cardiotoxicity, which is more frequent when high total doses (more than 25 to 30 mg/kg) are given, become a limiting factor clinically (8). Therefore, further attempts have been made to explore more active and less toxic antitumor agents. ACR was found to be less cardiotoxic as compared to two preparations of glycoside antibiotics, DNR and ADM. Previous work from our clinic showed that complete remission was obtained in 3 of 7 patients with refractory AML by ACR alone. In the present study, complete remission was obtained in 7 of 9 patients with a relapse of AML treated with the ACR-ara-C regimen. The results indicate the effectiveness of ACR in combination with ara-C on refractory AML. Further studies are needed to document the therapeutic superiority of ACR over DNR.

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