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# Acute Myelogenous Leukemia: Successful Treatment of Relapse with Cytosine Arabinoside, VP 16-213, Vincristine and Vinblastine (A-Triple-V)

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**Abstract**—*Between March* 1980 *and January* 1982, 15 *patients with acute myelogenous leukemia (AML) in relapse were treated with one or more cycles of a combination chemotherapy consisting of cytosine arabinoside(Ara-C), VP* 16-213, *vincristine and vinblastine (A-triple-V). Of a total of* 20 *treatment cycles given, one partial and* 15 *complete remissions were achieved, there was no change in the bone marrow in two cases, one patient died due to* Pseudomonas *septicemia during an apparently normal bone marrow regeneration and one patient died of* Candida *infection while in aplasia. With* 15 *out of* 20 (75%) *successful relapse treatment courses, A-triple-V should be tested in first-line protocols.*

## INTRODUCTION

MOST patients in remission from acute myelogenous leukemia (AML) will suffer a relapse of their disease within two years [1]. Today, two approaches to treatment for an AML relapse are employed: either reapplication of the same drugs used for the first successful induction or use of new experimental treatments. The first approach, while favored [2], frequently cannot be applied due to cumulative anthracycline toxicity.

All our relapse patients had their first complete remission (CR) induced by a combination treatment with daunorubicine (DNR), cytosine arabinoside (Ara-C) and vincristine [3]. This same regimen, however, could not be used again since the total dose of DNR (an anthracycline) had reached toxic levels. This drug was therefore replaced by VP 16-213, an agent active against AML both as a single substance [4, 5] and in combination with other medicaments [6, 7]. In addition, vinblastine was incorporated into the treatment due to its cytostatic activity in certain myelogenous leukemias [8].

With this relapse protocol (Ara-C, VP 16-213, vincristine and vinblastine: A-triple-V) a response rate similar to that of primary treatment of AML was obtained [1, 3].

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## MATERIALS AND METHODS

### *Patients*

Between March 1980 and January 1982, 15 patients suffering from a relapse of AML who entered the University Hospital of Zürich were given A-triple-V treatment in an attempt at inducing a second, third, fourth, fifth or sixth remission. Three patients received two cycles of A-triple-V and one received three cycles. Therefore, in these 15 patients, 20 relapses were treated. Age, sex, FAB classification of AML [9], percentage of leukemic blasts in the bone marrow at the time of relapse, time since the last cytostatic treatment, previous remission time and response to A-triple-V are shown in Table 1. Median age was approximately 50 yr, with a range of 24–65 yr. All patients were previously treated with Ara-C, DNR (minimal total dose was 495 mg/m$^2$) and vincristine. In addition, patients 1, 2, 3, 7, 8, 9, 11, 12, 13 and 15 had received 6-thioguanine and prednisone.

### *Prerequisites for A-triple-V treatment*

Appropriate measures were taken to control any systemic infection. Renal function had to be within normal limits. Uric acid complications

*Table 1. Characteristics of patients at the time of AML relapse and response to A-triple-V treatment*

| Patient No. | Age/ sex | Diagnosis (FAB lit. 3) | Percentage of leukemic blasts in bone marrow | Time since last treatment (months) | Previous remission time (months) | Response |
|---|---|---|---|---|---|---|
| 1 3rd relapse | 31 F | M2 | 28 | 12 | 84 | CR |
| 1 4th relapse | 32 F | M2 | 20 | 9 | 8 | CR |
| 1 5th relapse | 32 F | M2 | 38 | 6 | 5 | CR |
| 2 | 64 F | M5b | 30 | 3 | 32 | CR |
| 2 2nd relapse | 65 F | M5b | 55 | 12 | 11 | CR |
| 3 | 52 M | M4 | 50 | 38 | 70 | CR |
| 3 2nd relapse | 53 M | M4 | 47 | 16 | 14 | CR |
| 4 | 59 M | M6 | 51 | 14 | 16 | CR |
| 5 | 37 F | M2 | 71 | 3 | 7 | CR |
| 6 2nd relapse | 62 F | M2 | 90 | 6 | 14 | died |
| 7 | 45 M | M3 | 35 | 17 | 34 | CR |
| 7 2nd relapse | 46 M | M3 | 72 | 8 | 7 | PR |
| 8 | 59 F | M1 | 70 | 2 | 9 | NC |
| 9 | 49 F | M3 | 60 | 1 | 13 | NC |
| 10 | 58 M | M4 | 22 | 24 | 27 | died |
| 11 | 57 F | M3 | 37 | 2 | 11 | CR |
| 12 | 39 F | M4 | 48 | 2 | 6 | CR |
| 13 | 59 F | M5b | 28 | 7 | 31 | CR |
| 14 | 40 F | M2 | 33 | 18 | 21 | CR |
| 15 | 24 F | M5a | 87 | 22 | 46 | CR |

CR = complete remission; PR = partial remission (normal peripheral hematology, but still leukemic cells in bone marrow); NC = no change of bone marrow.

were prevented by allopurinol treatment and urine alkalinization.

*Treatment protocol*

The protocol for treatment is shown in Table 2. Care was taken that the infusion of Ara-C was as continuous as possible during days 1–7. VP 16-213 was diluted in 250 ml of isotonic sodium chloride solution and infused over a period of 30 min.

*Supportive therapy*

Patients were maintained with conventional hospital isolation. Infections of unknown etiology were treatment by a combination of a cephalosporine and an aminoglycoside antibiotic. Fungal infections were treated by amphotericin B and 5-fluorocytosine. Transfusions of erythrocytes and platelets were given when required. HLA-matched platelets were given to patients refractory to random platelets.

*Table 2. A-triple-V treatment for AML relapse*

| Drug | Dosage ($mg/m^2$) | Route | Day |
|---|---|---|---|
| Ara-C | 100 | continuous i.v. infusion | 1–7 |
| VP 16–213 | 100 | 30 min i.v. infusion | 1–5 |
| Vincristine | 0.8 | i.v. | 10 |
| Vinblastine | 6 | i.v. | 12 |

Ara-C = cytosine abarinoside.

*Evaluation of response and further treatment*

Following A-triple-V treatment, bone marrow was aspirated on days 28, 60, 90 and 120, and thereafter at intervals of 8 weeks. Complete remission was defined according to the CALGB criteria [10].

No maintenance treatment was given. In case of relapse, reinductions with A-triple-V were performed if possible.

## RESULTS

*Response*

Fifteen of the 20 A-triple-V treatment cycles were successful in patients suffering from AML in relapse (see Table 1). At day 28 after treatment, patients 1, 2, 3, 5, 12, 13 and 15 already showed a bone marrow remission, whereas in patients 4, 7, 11 and 14 a normal bone marrow could only be detected at day 60. In these 4 patients on day 28, their marrow contained numerous immature or undifferentiated elements and thus made a distinction between a regenerating or a leukemic bone marrow im-

possible. Approximately four weeks after the detection of a bone marrow remission, the peripheral hematological values also returned to normal.

Of the AML patients who did not attain CR, patients 8 and 9 had bone marrow smears with approximately the same percentage of leukemic blasts before and after treatment. Following a second cycle of A-triple-V, patient 7 achieved only a partial remission, with a normal blood picture but leukemic cells in the bone marrow. Patient 6, a 62-year-old woman in her second AML relapse, died from *Pseudomonas* septicaemia on day 20, when the granulocytes were already above 2000/mm$^3$. Patient 10 died from a generalized *Candida* infection on day 12 while in aplasia. A summary of patient responses to A-triple-V is given in Table 3.

*Drug toxicity*

Bone marrow function was profoundly depressed in all patients following therapy with A-triple-V. Granulocytopenia and thromobocytopenia lasted from 15 to 35 days (see Table 4). A rise in platelets usually preceded granulocytes by a few days. Minor incidences of paralytic ileus due to the vinca alkaloids developed in about half of the patients between days 14 and 18. Episodes of slight nausea infrequently occurred during the first seven days of treatment; vomiting was rarely observed.

*Remission duration and survival*

Remission duration and survival data are presented in Table 5. Patient 1 relapsed eight months after her first A-triple-V cycle and five months after a second cycle. A third CR was achieved with the following amended treatment schedule: Ara-C 100 mg/m$^2$ in continuous infusion on days 1 and 2, VP 16-213 80 mg/m$^2$ on days 3–7, 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (*m*-AMSA) 80 mg/m$^2$ on days 3–7, vinblastine 6 mg/m$^2$ on day 10. A second A-triple-V cycle produced a CR in patients 2 and 3 and a PR in patient 7. Patients 4 and 12, who attained CR following A-triple-V, refused a second cycle for a second relapse. Patient 11 left the country, so no further treatment was possible.

*Table 3. Results of A-triple-V treatment in AML relapse*

| |
|---|
| 20 treatment cycles in 15 patients |
| 15 complete remissions (75%) |
| 1 partial remission (normal peripheral hematology) |
| 2 deaths during reinduction treatment (infections) |
| 2 nonresponders |

*Table 4. Days of granulo- and/or thrombocytopenia**

| Patient No. | Number of days |
|---|---|
| 1 (first A-triple-V) | 20 |
| 1 (second A-triple-V) | 18 |
| 1 (third A-triple-V + *m*-AMSA) | 35 |
| 2 | 18 |
| 2 (second A-triple-V) | 22 |
| 3 | 21 |
| 3 (second A-triple-V) | 21 |
| 4 | 35 |
| 5 | 20 |
| 7 | 21 |
| 7 (second A-triple-V) | 27 |
| 11 | 30 |
| 12 | 28 |
| 13 | 15 |
| 14 | 22 |
| 15 | 30 |

*Granulocytes $< 500/mm^3$ and/or thrombocytes $< 20{,}000/mm^3$.

## DISCUSSION

The A-triple-V treatment for AML in relapse produced second, third, fourth, fifth and sixth remissions in 15 of 20 trials (75%). Compared to other relapse treatments, this response rate is one of the best ever observed. For example, with combinations of Ara-C, anthracyclines and 6-thioguanine, only 50–60% of patients achieve CR after a first AML relapse [2, 11].

In explanation of our results, two questions must first be addressed: first, did our relapse patients belong to a favorable prognostic group, and second, was the A-triple-V treatment itself especially efficacious?

Regarding the first point, the preponderance of females in our small group proved not to be a favorable prognostic factor [11] since both sexes achieved CR in similar proportions. On the other hand, the relatively long previous remission time could be considered a favorable prognostic factor.

Unfavorable prognostic factors included relapse after an intensive pretreatment with a combination of DNR and Ara-C, and age (median 50 yr).

The A-triple-V treatment itself appears to make the key contribution to the high response rate. Taking into account the cytostatic properties of the drugs and their sequence of application, several factors could explain the efficacy of A-triple-V treatment in AML relapse: all our patients were exposed to Ara-C

*Table 5. Remission duration and survival*

| Patient No. | Remission duration (months)* | Survival (months) | |
|---|---|---|---|
| 1 (first A-triple-V) | 8 | | |
| 1 (second A-triple-V) | 5 | | |
| 1 (third A-triple-V + *m*-AMSA) | 4 | 21† | |
| 2 | 11 | | |
| 2 (second A-triple-V) | 6† | | |
| 3 | 14 | | |
| 3 (second A-triple-V) | 2† | | |
| 4 | 4 | 9 | |
| 5 | bone marrow transplantation | 3 | (post-transplantation pneumonia normal bone marrow) |
| 7 | 7 | | |
| 7 (second A-triple-V) | 3 | 15 | |
| 11 | 3 | 6 | |
| 12 | 2 | 4 | |
| 13 | 7 | 10† | |
| 14 | 8+ | | |
| 15 | 1 | 3† | |

*Counted from the normalization of the bone marrow.
†Remission continues, alive.

in their earlier successful induction treatments, and drugs which are effective in treating newly-diagnosed AML patients are frequently also efficacious in reinduction [2]. VP 16-213 is active against AML as a single substance [4, 5], as well as in combination with other medicaments [6, 7]. In addition, this agent may also potentiate the activity of Ara-C, a phenomenon reported in an animal model [12]. The efficacy of vincristine in A-triple-V treatment is probably dependent on its time of application following Ara-C treatment. Studies on sequential therapy of AML have shown that vincristine should be given one to several days after the Ara-C, when mitotic activity of residual leukemic cells is most pronounced [13, 14]. Vincristine was administered on day 10 and vinblastine on day 12 since maximal mitotic activity after the Ara-C infusion may occur only after day 10. Vinblastine, in addition, has a well-known myelosuppressive activity and has been shown to be active in certain types of AML in children [8].

As is the case whenever combination chemotherapies are employed, it is difficult to determine the paramount factors determining a treatment's efficacy. Factors relevant to the success of the A-triple-V combination could be: (1) the simultaneous application of Ara-C and VP 16-213; (2) the addition of the two vinca alkaloids; or (3) the A-triple-V program as a whole. Since the treatment is well-tolerated, there is no need to reduce or to omit any part of this combination chemotherapy. Furthermore, since A-triple-V is an anthracycline-free combination, it can be used not only for most relapse patients irrespective of previous therapy but also for older patients and patients with cardiac problems.

With occasional exceptions [15], none of the chemotherapeutic agents introduced recently have resulted in CR rates of over 25% [16, 17]. Our results show that a first or even a second relapse of AML is best treated with combination chemotherapies such as A-triple-V, and not with single experimental drugs. In addition, our data suggest that an extensive testing of A-triple-V in the primary treatment of AML is warranted.

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