Cancer Chemother Pharmacol (1981) 6:65–73

Cancer Chemotherapy and Pharmacology



# Comparison of Daunorubicin and Daunorubicin-DNA Complex in the Treatment of Acute Nonlymphoblastic Leukemia

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***Summary.*** *Sixty consecutive patients, 15–60 years old, with ANLL were divided randomly into three groups for induction treatment with one of the following regimens: R1, daunorubicin (DNR) 1.5 mg/kg on day 1 + ARA-C 2 mg/kg body weight on days 1–5; R2, DNR 1.5 mg/kg on days 1 and 2 + ARA-C 2 mg/kg on days 4–8; R3, DNR-DNA complex 1.5 mg/kg on days 1 and 2 + ARA-C 2 mg/kg on days 4–8. Maintenance treatment consisted of monthly courses of DNR 1.5 mg/kg (R1, R2) or DNR-DNA 1.5 mg/kg (R3) combined with ARA-C 1 mg/kg on days 1–5, alternating with thioguanine 2 mg/kg PO on days 1–5 combined with ARA-C 1 mg/kg IV on days 1–5. Fourteen patients of 20 went into complete remission with R1, 13 of 18 with R2, and 15 of 22 with R3. The overall remission frequency was 70% and there was no significant difference between the different groups. The median time in first remission and the median survival time were 300 and 510 days, respectively, with R1; 335 and 495 days with R2; and 295 and 677 days with R3. There was no statistically significant difference between the groups treated according to the different regimens concerning the time in first remission. Survival was slightly better with R3 than with R1. Treatment with the DNR-DNA complex caused less pronounced thrombocytopenia and fewer 'minor' cardiac abnormalities than treatment with free DNR in the same dosage schedule.*

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## Introduction

Daunorubicin (DNR) is an effective drug for inducing remission in acute leukemia [1, 4, 15, 16, 29, 30]. Except for bone marrow depression, acute or chronic cardiotoxicity is the most important side-effect [2, 11–13, 20]. Although such acute cardiotoxicity occasionally gives rise to fatal arrhythmias or sudden heart failure, the chronic cardiotoxicity has even greater clinical importance, since it restricts the use of the drug in maintaining remission. The mechanism behind the cardiotoxicity is still not clear.

In 1972, Trouet et al. introduced the idea of lysosomotropic cancer chemotherapy, based on the findings of de Duve regarding the properties of the lysosomes [27]. By administering an anthracycline complex-bound to DNA, it was thought that the drug would enter the cell by endocytosis, a more specific process than diffusion. In this way the effect of the drug on cells with a low endocytotic capacity, e.g., myocardial cells, would be reduced. The theory was supported by experimental findings [17, 28] and preliminary results showed that DNR-DNA complex was effective against acute leukemia [3, 19, 25, 26].

In 1976 the Leukemia Group of Central Sweden (LCS) decided to evaluate the DNR-DNA complex for the treatment of acute nonlymphoblastic leukemia (ANLL) in a randomized trial. The study also included a comparison of a more intensive induction treatment program with a milder one. Some of the results have been presented earlier [9].

0344-5704/81/0006/0065/$ 01.80

## Materials and Methods

*Patients*

Practically all patients aged 15–60 years who had previously untreated ANLL and who belonged to the catchment area of the LCS (population about 2 million) were included in the study. Patients with smouldering leukemias were excluded. Immediately after the diagnoses had been made the patients were reported to the treatment center and assigned randomly to one of three treatment groups (R1, R2, R3) described below. The age and sex distribution of the patients is shown in Fig. 1. The classification according to subgroups of ANLL is given in Table 1.

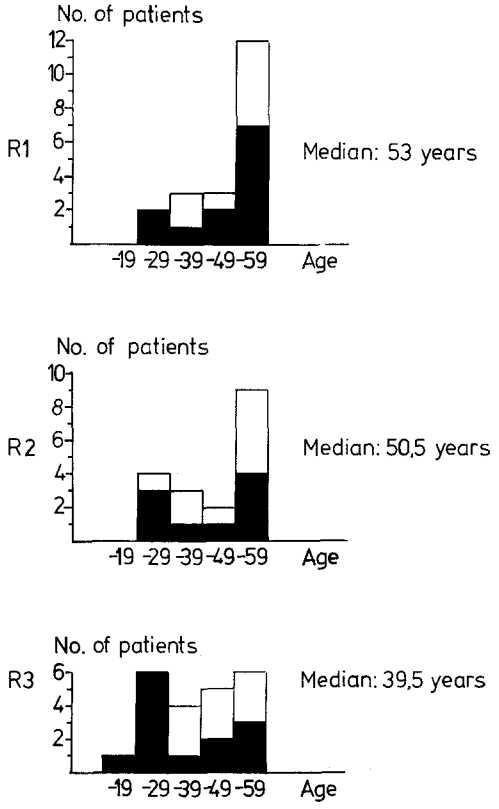


**Fig. 1.** Age and sex distribution of patients treated with DNR (R1, R2) or DNR-DNA complex (R3). *Filled bars,* male; *open bars,* female

**Table 1.** Distribution of morphological types of ANLL in the treatment groups

| Type of leukemia | Number of patients on treatment program | | |
|---|---|---|---|
| | R1 | R2 | R3 |
| Acute myeloblastic leukemia (M1, M2) | 13 | 14 | 17 |
| Acute promyelocytic leukemia (M3) | 2 | 0 | 0 |
| Acute myelomonocytic leukemia (M4) | 4 | 2 | 5 |
| Acute monocytic leukemia (M5) | 1 | 1 | 0 |
| Acute erythroleukemia (M6) | 0 | 1 | 0 |

**Treatment Schedules**

*Induction Treatment*

*R1.* DNR 1.5 mg/kg (push) on day 1 and ARA-C 1 mg/kg IV twice daily on days 1–5. After an interval of 5 days the course was repeated until complete remission or bone marrow hypoplasia occurred. In cases of severe bone marrow depression the drug-free interval was extended until the white blood cell (WBC) count was above $1.0 \times 10^9$/l. If progression of the leukemia occurred after three courses, a second dose of DNR (1.5 mg/kg) was given on day 2 in the fourth course, and if progression continued a third dose of DNR was given on day 3 during the fifth and sixth courses.

*R2.* DNR 1.5 mg/kg as a 4-h infusion on days 1 and 2; day 3 drug-free; ARA-C 1 mg/kg IV twice daily on days 4–8; and days 9–16 drug-free. The course was repeated from day 17 until a complete remission was achieved. If bone marrow hypoplasia occurred, the drug-free interval between the courses was extended as in R1. If the leukemia had progressed after the fourth course, DNR 1.5 mg/kg was given on day 3.

*R3.* Identical with R2 except that DNR-DNA complex was given at a rate of 100 ml/h (infusion time about 4–6 h) instead of DNR.

If a patient did not respond after six courses of treatment according to one of the above schedules it was regarded as a failure and treatment was changed to COAP [31].

*Maintenance Therapy*

The patients were maintained with alternating monthly courses of DNR (or DNR-DNA complex) 1.5 mg/kg on day 1 + ARA-C 1 mg/kg on days 1–5 and thioguanine 2 mg/kg PO on days 1–5 + ARA-C 1 mg/kg IV on days 1–5. Those patients who had been induced with DNR-DNA complex were also maintained with DNR-DNA complex, while those who had been induced with DNR were maintained on the free drug. In R1 and R2, maintenance treatment with DNR was withdrawn when the patients had received a cumulative dose of 20 mg/kg body weight, corresponding to about 650–800 mg/m$^2$. In R3 the responsible physician was allowed to exceed this maximum limit until there were signs of cardiotoxicity. However, in most cases DNR-DNA was withdrawn at the same dose level as in the other two groups.

*Relapse Treatment*

When the patients relapsed, VAMP courses [8] were given in an attempt to induce a second remission.

*Immunotherapy*

After a complete remission had been achieved the patients were randomly divided into groups which received maintenance chemotherapy either alone (Ch) or in combination with immunotherapy with BCG and live allogeneic leukemia cells (ChIm) [18]. Patients receiving immunotherapy were evenly distributed between R1, R2, and R3, i.e., five, six, and six patients, respectively, were assigned the individual groups.

*Definition of Remission*

Patients were regarded as being in complete remission if the bone marrow contained no more than 5% blast cells and if their

peripheral blood granulocyte and platelet counts were at least $1.5 \times 10^9$/l and $100 \times 10^9$/l, respectively, after recovery from the hematologic toxicity of the treatment program. Patients were considered to be in partial remission if their bone marrow contained 6%–40% blast cells, their blood contained < 5% blast cells, and their peripheral blood granulocyte and platelet counts were $0.5-1.5 \times 10^9$/l and $25-100 \times 10^9$/l, respectively.

*Definition of Myelosuppression*

A decrease of the platelet count to less than $10 \times 10^9$/l and WBC count to $1.0 \times 10^9$/l during induction was defined as severe myelosuppression (Table 7). Since many of the patients were thrombocytopenic and leukopenic before treatment, the time for a decrease of platelets and WBC to 50% and 10%, respectively, of the pretreatment values was also determined.

*Laboratory Controls*

During induction treatment, hemoglobin concentration, platelet count, and WBC count were checked daily and other laboratory parameters, including differential count, serum creatinine, and serum liver tests, once weekly. These parameters were also determined before the monthly maintenance courses. Bone marrow examination was in most cases performed after each induction course and before each maintenance treatment course.

*Heart Examinations*

Besides frequent clinical examinations, ECG was checked weekly during induction treatment and before each maintenance course. Heart X-ray was performed before treatment was started, and thereafter if clinically indicated before every additional DNR infusion and when the patients had received 15 mg DNR/kg body weight. At three of the participating hospitals systolic time interval (STI) determinations were performed regularly. All signs of cardiac abnormalities that appeared during or after DNR treatment were registered as possible toxic effects. They were divided into two groups. Benign arrhythmias with no therapeutic consequences, such as sinus tachycardia, sinus bradycardia, ectopic rhythm, extrasystoles, ST-T changes in the form of flattening or inversion of T-wave and S-T depression or elevation, were regarded as 'minor' abnormalities. 'Major' cardiac manifestations included development of heart incompensation, more severe arrhythmias, such as flutter and fibrillation, and light-microscopical findings at autopsy which were not incompatible with DNR-induced damage (Tables 5 and 6).

*Preparation and Administration of the DNR-DNA Complex*

DNA (herring sperm DNA type VII, Sigma St. Louis, USA) was dissolved in saline to give a concentration of 2.34 mg DNA/ml. The solution was heated to 95° C and then filtered through a 0.8-μm Millipore filter. This solution was stored for not more than 6 months at the hospital pharmacy concerned. About 12 h before use, the solution was autoclaved at 120° C for 15 min and then left to cool slowly: it was used not later than 24 h after autoclaving. DNR (Cerubidine, Leo Rhodia, Helsingborg, Sweden) was dissolved in saline to give a concentration of 20 mg/ml and was then added to the DNA solution. The DNR-DNA complex solution was administered IV during 4–6 h at a rate of about 100 ml/h.

*Statistical Tests*

Differences between the groups in frequency of remission, cardiac complications and toxic effects were evaluated with Fischer's exact test. Time to remission, length of first remission, and survival were calculated by actuarial analysis. Differences in these parameters were evaluated with Fischer's exact test.

## Results

### *Remission Induction*

A complete remission was induced in 14 of 20 patients with R1, 13 of 18 with R2, and 15 of 22 with R3. The overall rate of complete remission was 70% and there were no differences between the treatment groups (Table 2). Of the adequately treated patients (i.e., patients treated for more than 2 weeks) 14 of 19 with R1, 13 of 18 with R2, and 15 of 20 with R3 had achieved a complete remission. Thus the frequency of complete remissions was 74% in these patients.

Compliance with the program was mainly good, but five patients (two receiving R1, one R2, and two R3) received additional cytostatic treatment before they achieved a complete remission. One patient in the R1 group was switched over to vincristine combined with prednimustine, due to severe leukopenia. One patient in the R3 group was switched to VAMP treatment because he refused further treatment with DNR. Two patients, one in the R1 and one in the R3 group, each received one course of VAMP, and one patient in the R2 group received two courses of VAMP before complete remission, but their maintenance treatment was according to the program. These five patients had responded to the original treatment and were near complete remission, with 5%–10% myeloblasts in the bone marrow.

There was a tendency to a larger number of induction courses with R1 than with R2 and R3 (Fig. 2), but the dose of DNR needed for a complete remission (Table 3) was somewhat lower with R1 than with R2 and R3. There were no statistically

**Table 2.** Induction of complete remissions in the three treatment groups

| | Treatment groups | | |
|---|---|---|---|
| | R1 | R2 | R3 |
| Total number of patients | 20 | 18 | 22 |
| Number of complete remissions | 14 (70%) | 13 (72%) | 15 (68%) |
| Number of complete remissions in patients treated for at least 2 weeks | 14/19 (74%) | 13/18 (72%) | 15/20 (75%) |

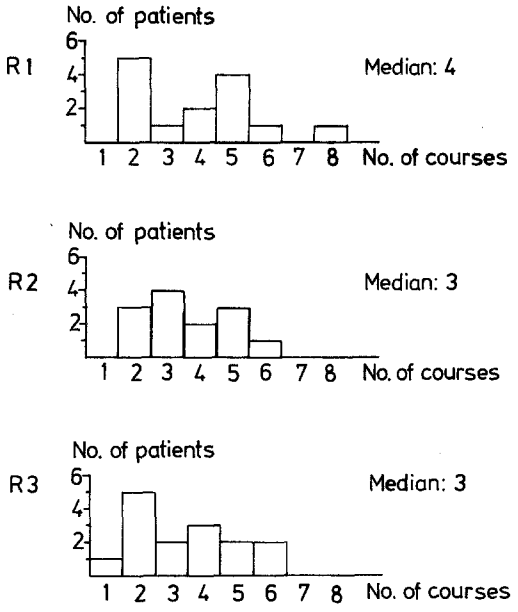


**Fig. 2.** Number of treatment courses given to achieve complete remission in patients treated with DNR (R1, R2) or DNR-DNA complex (R3)

**Table 3.** Dose of DNR (mg/m$^2$) to complete remission in the three treatment groups

| | Treatment groups | | |
|---|---|---|---|
| | R1 | R2 | R3 |
| Median | 225 | 395 | 300 |
| Range | 90–540 | 190–600 | 100–630 |

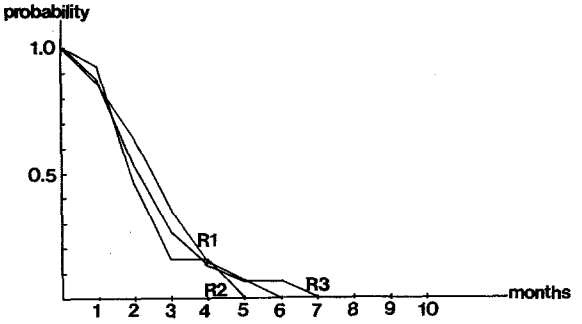


**Fig. 3.** Time to complete remission in patients treated with DNR (R1, R2) or DNR-DNA complex (R3)

significant differences between the treatment groups in the time to complete remission (Fig. 3). One patient in the R1 group, two in the R2 group, and three in the R3 group had a second remission, and of these two patients receiving the R3 regimen had a third remission.

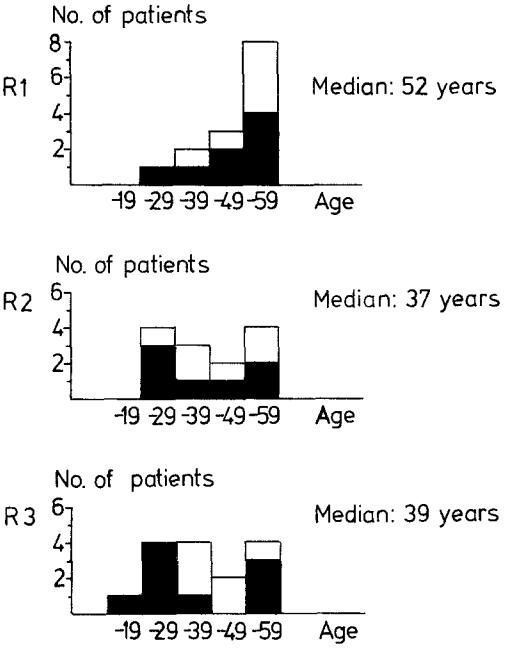


**Fig. 4.** Age and sex distribution of patients achieving complete remissions after treatment with DNR (R1, R2) or DNR-DNA complex (R3). *Filled bars,* male; *open bars,* female

### *Frequency of Remission in Relation to Age*

The age distribution of all patients is shown in Fig. 1 and that of patients in remission in Fig. 4. Higher age was not correlated to lower remission frequency for patients treated according to R1 and R3, while there was a tendency for the older patients to have a lower response rate in the R2 group.

### *Causes of Death in Patients Without Remission*

To evaluate whether there was a higher frequency of deaths due to severe hypoplasia with septicemia and bleeding with the more intensive treatment programs (R2 and R3), the causes of death in patients without remission were analysed. The results are presented in Table 4. There was no significant difference between the groups in the frequency of death due to severe hypoplasia.

### *Duration of Remission*

The median duration of the first remission was 300 days in R1, 335 days in R2, and 295 days in R3. The length of the first remission did not differ significantly between the treatment groups (Fig. 5).

**Table 4.** Causes of death in patients without remissions

| | Treatment groups | | |
|---|---|---|---|
| | R1 | R2 | R3 |
| Total number of patients | 20 | 18 | 22 |
| Number of patients without remission | 6 | 5 | 7 |
| Severe bone marrow hypoplasia with septicemia and bleedings | 1 | 3 | 2 |
| Septicemia without severe bone marrow hypoplasia | 2 | 1 | 3 |
| No response | 2 | 1 | 2 |
| Pulmonary embolism | 1 | 0 | 0 |

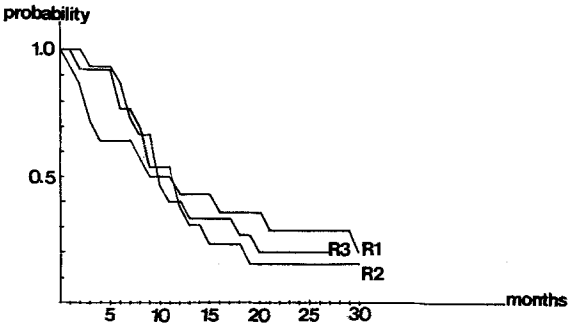


**Fig. 5.** Duration of first remission in patients treated with DNR (R1, R2) or DNR-DNA complex (R3)

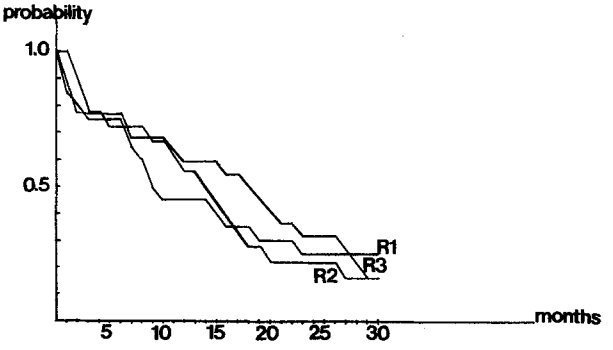


**Fig. 6.** Survival of all patients after treatment with DNR (R1, R2) or DNR-DNA complex (R3)

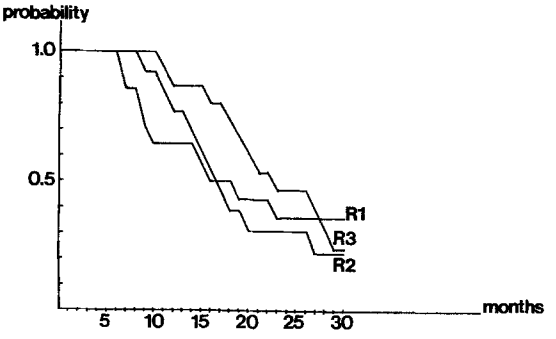


**Fig. 7.** Survival of patients who achieved complete remission after treatment with DNR (R1, R2) or DNR-DNA complex (R3)

**Table 5.** Number of patients with cardiac complications and mean cumulative DNR dose in the three treatment groups

| | Treatment groups | | |
|---|---|---|---|
| | R1 | R2 | R3 |
| Total number of patients | 20 | 18 | 22 |
| Number of patients with cardiac complications | 8 | 12 | 6 |
| Per cent with cardiac complications | 40 | 67 | 27 |
| DNR, total dose ($mg/m^2$) mean ± SD | 331 ± 236 | 546 ± 228 | 606 ± 358 |

### *Survival*

The median survival time for all patients was 270 days in R1, 420 days in R2, and 540 days in R3 (Fig. 6). The median survival time for patients in complete remission was 510 days in R1, 495 days in R2, and 675 days in R3 (Fig. 7). At 9 and 10 months the survival of patients in remission in the R3 group was significantly longer ($P < 0.05$) than in the R1 group. Other differences in survival between the groups were not statistically significant. Twenty-six months after the study was completed twelve patients were still alive, nine of whom were in complete remission.

### *Cardiotoxicity*

In 16 patients (43%) cardiac abnormalities appeared that could be related to the DNR treatment (Table 5). Of these, 14 patients also had signs of major cardiac abnormalities (Table 6). Manifestations of cardiac abnormalities were least frequent in those treated with DNR-DNA and most frequent in those treated according to R2 (Table 5) ($P < 0.05$). The difference in favour of R3 accentuated if the frequency of cardiac abnormalities is related to the cumulative mean dose of DNR in the different treatment groups. The difference in cardiac manifestations was restricted to minor cardiac abnormalities and there was no significant difference between the treatment groups as regards major cardiac abnormalities (Table 6).

### *Myelosuppression*

The most pronounced drop in platelet count was seen in R2. In 17 of 18 patients in this group the platelet count decreased to less than $10 \times 10^9/l$, whereas a similar drop was seen in only slightly more than half of the patients in R1 and R3. This difference between

**Table 6.** 'Major' cardiac manifestations in patients with ANLL treated with daunorubicin or daunorubicin-DNA[a]

| Treatment groups | Patient | | | Cumulative dose mg/m$^2$ | Symptoms and signs | Autopsy | Comment |
|---|---|---|---|---|---|---|---|
| | No. | Age | Sex | | | | |
| R1 | 134 | 38 | M | 450 | ST-T abnormalities, sinus tachycardia. Radiological and clinical signs of heart failure | Macro: Subendocardial bleedings. Micro: Not performed | The patient was in relapse. Platelet count was $68 \times 10^9$ |
| | 145 | 53 | F | 278 | ST-T changes of left ventricular leads. Moderate increase in heart volume on X-ray | Not performed | The patients was in relapse |
| | 154 | 28 | M | 630 | Increased heart volume on X-ray after maximum dose of DNR (630 mg/m$^2$). Inversion of T-wave after first course | | Patient alive in remission. Heart volume increase and ECG changes reversible |
| | 157 | 52 | M | 700 | 2 : 1 blocked flutter ST-T abnormalities | Not performed | The patients was in relapse |
| | 182 | 59 | M | 535 | ST-T abnormalities | Micro: Fibrosis of myocardium | |
| R2 | 137 | 59 | F | 690 | Progressive ST-T changes | Blast cell infiltration in myocardium. Subendocardial bleedings | The patient was in relapse at death. In remission at start of ST-T changes |
| | 159 | 57 | F | 370 | Flattening of T-wave | Micro: Focal necrosis in the myocardium | Patient in relapse. Died in sepsis |
| | 168 | 27 | M | 750 | Inversion of T-wave. Clinical and radiological signs of heart failure | Not performed | After the second course. Possibly pericarditis. The patient was not in remission |
| | 179 | 48 | F | 630 | Increase of heart volume after the first course. Death in cardiac failure | Macro: Dilated heart. Micro: Not performed | Not in remission when signs of cardiac failure |
| | 189 | 34 | F | 605 | Clinical and radiological signs of heart failure | Fibrosis of myocardium | The patient was not in remission. Reduction of DNR in the courses thereafter |
| R3 | 140 | 59 | F | 650 | Clinically no signs | Micro: Increase of lipofuscin in myocardium. No other signs of DNR-induced damage | |
| | 166 | 46 | F | 470 | Sinus tachycardia during courses | Not performed | Sinus tachycardia initially. DNR therapy withdrawn |
| | 175 | 39 | F | 700 | Clinically no signs | Micro: Increase of lipofuscin in myocardium | |

[a] Cumulative dose, total dose received by patient; Macro, macroscopical findings; Micro, findings in the light microscope

**Table 7.** Myelosuppression in patients with ANLL treated with DNR or DNR-DNA combined with ARA-C

| | Treatment group | | |
|---|---|---|---|
| | R1 | R2 | R3 |
| Total number of patients | 20 | 18 | 22 |
| Number of patients with WBC decrease to $1.0 \times 10^9$/l | 13 | 15 | 20 |
| Number of patients with platelet decrease to $10 \times 10^9$/l | 13 | 17 | 13 |
| Mean time in days to platelet decrease below 50% of pretreatment value | 5.7 ± 2.7 | 3.7 ± 2.1 | 6.9 ± 3.7 |
| Mean time in days to platelet decrease below 10% of pretreatment value | 10.1 ± 1.3 | 7.4 ± 3.0 | 10.4 ± 2.1 |
| Mean time in days to WBC decrease below 50% of pretreatment value | 2.9 ± 1.5 | 1.8 ± 0.9 | 2.1 ± 1.5 |
| Mean time in days to WBC decrease below 10% of pretreatment value | 7.9 ± 4.7 | 4.5 ± 3.3 | 3.8 ± 2.0 |

**Table 8.** Number of patients with toxic manifestations related to treatment with DNR and DNR-DNA excluding myelosuppression and cardiac abnormalities

| | Treatments groups | | |
|---|---|---|---|
| | R1 | R2 | R3 |
| Total number of patients in the treatment groups | 20 | 18 | 22 |
| Nausea and vomiting | 6 | 12 | 8 |
| Liver damage S-ASAT and S-ALAT increase | 5 | 6 | 4 |
| Fever | 6 | 4 | 2 |
| Alopecia | 2 | 4 | 1 |
| Chills | 2 | 1 | 0 |
| Diarrhea | 2 | 1 | 1 |
| Allergic skin reactions | 0 | 2 | 0 |
| Allergic phlebitis | 0 | 1 | 0 |
| Muscle ache | 0 | 1 | 1 |
| Total | 23 | 32 | 17 |

R2 and R3 was statistically significant ($P < 0.05$). There was also a tendency to a faster decrease in platelet count in R2 compared with R1 and R3. There was no difference between the number of patients whose WBC dropped below $1.0 \times 10^9$/l but there was a tendency for a slower fall in WBC with R1 than with R2 and R3 (Table 7).

### *Other Toxic Effects*

Nearly half the patients had severe nausea. This was most pronounced in R2, where 12 of 18 patients had nausea. Twenty-five percent had an elevation of liver transaminases, but there was no difference between the three groups as regards signs of liver toxicity. Other side-effects reported included allergic skin reaction in two patients, one with skin necrosis leading to interruption of DNR therapy. The total numbers of reported toxic effects other than myelosuppression and cardiac abnormalities related to DNR therapy were 23, 32, and 16 in R2, R2 and R3, respectively (Table 8).

## Discussion

The administration of daunorubicin combined with ARA-C is an effective and established way of inducing remission in ANLL [4, 16, 30]. Since 1973 the Leukemia Group of Central Sweden has used this drug combination with good results [9, 29]. In the present study one group of patients (R1) received this treatment in 5-day courses, with an initial interval of 5 days between courses and DNR on only the first day of the course at a dosage of 1.5 mg/kg. In recent years it has been reported that more aggressive induction treatment may lead to a higher remission frequency [10]. Therefore, one group of patients was given more intensive treatment (R2). DNR was given for 2 days, each day at the same dosage as previously used, and ARA-C for 5 days, with an interval of 1 day between DNR and ARA-C.

Daunorubicin is an agent that intercalates between base pairs in the DNA double helix and blocks further DNA synthesis. Theoretically, a 1-day interval between DNR treatment and ARA-C might allow DNA synthesis in cells not killed by DNR. This would increase the effect of ARA-C, a specific DNA synthesis-inhibiting antimetabolite. The results did not prove that this altered timing and more aggressive treatment was more effective than the one previously used by us. A higher death rate due to drug-induced hypoplasia would have hidden an improved antileukemic effect. However, the number of patients dying with septicemia or bleeding due to severe treatment-induced aplasia did not differ significantly between R1 and R2.

Since experimental data have indicated that the toxicity of DNR is reduced when complex-bound to DNA, the timing and dosage for the DNR-DNA treatment group were designed to be similar to those of the more intensive of the other two groups. The results show that the complex was at least as effective as the free drug. No significant differences were found between groups in the frequency or duration of remission, but the survival was somewhat better in R3

than in R1. The overall frequency of remission was high, about 70%, and the median survival time was comparable to that previously reported by LCS [18]. Previous reports by others have also shown a high incidence of remission with the DNR-DNA complex [3, 7]. Although the number of patients in these studies was small, one of them was randomized [7]. That study included 26 patients, 13 of whom were randomly selected to treatment with DNR-DNA 150 mg/m$^2$ for 24 h. The remission frequency and survival did not differ significantly between the two groups. Although the design of that study was different from ours, the results are consistent with our findings that the DNR-DNA complex is as effective as free DNR for inducing and maintaining remission in ANLL.

The main reason for using the DNR-DNA complex was the possibility of being able to reduce the cardiotoxicity of DNR. Our data support the view that DNR-induced cardiotoxicity may be decreased by complex-binding to DNA, without reducing the therapeutic efficacy of the drug. The total number of cardiac manifestations was significantly smaller in patients treated with the complex than in those treated with the free drug in programs that were otherwise identical (R3 compared with R2). When less free DNR (R1) was given the difference was not apparent. Our investigation did not provide evidence of a reduction of major cardiotoxicity, such as incompensation, severe arrhythmias, and morphological signs of heart muscle damage. Although five, five, and three patients, respectively, in the three treatment groups R1, R2, and R3 developed such complications, their relation to DNR (or DNR-DNA) treatment was uncertain. Most of these patients were not in remission and several had septic infections and anemia as factors contributing to the cardiac manifestations. In no case did the light-microscopical findings provide definitive evidence of DNR-induced cardiomyopathy.

A further difficulty in evaluation of the chronic cardiotoxicity of the DNR-DNA complex was that in most patients DNR-DNA was withdrawn before a cumulative 'high-risk' dose was reached. However, three patients, all treated with DNR-DNA received cumulative dosages exceeding 1,000 mg/m$^2$ (1,050, 1,075, and 1,353/m$^2$). Among these, the only heart complication was one episode of ectopic rhythm in one patient.

A few other reports have pointed to the possibility of using higher cumulative doses of DNR if the drug is complex-bound to DNA [7, 22, 28]. In our own report [22] we have presented evidence that patients who had shown signs of heart failure when treated with free DNR could be given DNR-DNA complex in total doses exceeding 1,200 mg/m$^2$ without new cardiotoxic manifestations. Thus, although not proven in the present study, it is likely that not only immediate cardiotoxic manifestations can be reduced by complex-binding, but also major, dose-dependent ones.

According to the lysosomotropic theory [27], the mechanism behind a reduced cardiotoxicity of the DNR-DNA complex should be a low level of endocytotic activity of the myocardial cells, compared with the malignant cells. The major objection to this previous view is that the DNR-DNA complex is dissociated to a relatively high degree in the plasma [5, 23, 24]. As these studies show, it is more likely that the DNR-DNA complex may serve as slow-release preparation of DNR with pharmacokinetics different from those of the free drug [6, 14, 23].

Other side-effect were mainly of the same kind in all treatment groups. However, induction of thrombocytopenia was less frequent and less pronounced in patients treated with the DNR-DNA complex. This may also be due to the change in pharmacokinetics due to the complex-binding of DNR.

Thus, complex-binding of DNR to DNA appears to have some advantages in the treatment of ANLL as against treatment with the free drug. It is possible that these advantages will be more pronounced if doxorubicin is used instead of DNR, since it has been shown that the DNA complex of the former is more stable in plasma and the differences between the pharmacokinetics in plasma and leukemic cells of the free and complex-bound drug are more pronounced for doxorubicin than for DNR [21, 23]. Studies are in progress to evaluate the possible therapeutic advantages of using the doxorubicin-DNA complex.

*Acknowledgements.* This study was supported by grants from the Swedish Cancer Society. We are indebted to Dr Staffan Ekblom for the statistical evaluation of the results and to Miss Åsa Johansson for excellent technical assistance.

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Received February 6/Accepted March 26, 1981