USE OF DNA IN MYLERAN-INDUCED CYTOPENIA

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Myleran was given by mouth in a single dose of 10 mg/kg or in doses totaling 25 mg/kg spread over 18 days to Wistar rats weighing 180-190 g. After receiving myleran, the animals were given four to five injections of homologous DNA on alternate days in a dose of 2 mg per rat or, alternatively, standard salt citrate. Under the influence of DNA the duration of leukopenia was reduced. The number of leukocytes in animals receiving the smaller dose of myleran returned to its initial level by the sixth day in the treated animals and by the 25th day in the untreated animals; after the larger dose of myleran the initial level was restored by the 15th and 25th days after the beginning of DNA injection, respectively. Differences in the number of leukocytes in the treated and untreated animals receiving the smaller and the larger doses of myleran were due mainly to the dynamics of the neutrophils, the numbers of which were greater in the treated than in the untreated rats by 54-110% in the first experiment in the period from 6 to 15 days, and by 23-38% in the second experiment in the period from 10 to 23 days after the beginning of DNA administration.

KEY WORDS: myleran; leukopenia; DNA administration.

DNA is known to stimulate hematopoiesis in healthy and irradiated animals [1-4, 9] and also to prevent the development of leukopenia in patients receiving radiotherapy or chemotherapy [12]. It was accordingly decided to study the effect of DNA on cytopenia induced by cytostatics.

EXPERIMENTAL METHOD

Experiments were carried out on 67 male Wistar rats weighing 180-190 g. Myleran was given by mouth to the animals: a single dose of 10 mg/kg in the first experiment, an 18-day course, with an initial dose of 10 mg/kg followed by doses of 5 mg/kg at 5-day intervals up to a total dose of 25 mg/kg in the second experiment. The animals of the experimental groups received intramuscular injections of 2 mg DNA 24 h after the end of myleran administration, whereas the animals of the control groups received standard salt citrate (SSC) on alternate days for 4 and 5 times, respectively, in the first and second experiments.

Preparations of DNA (molecular weight $29 \cdot 10^6$ daltons; protein 0.5%, RNA 1.5%) were obtained from rat thymus and spleen by a modified method [10]. The peripheral blood of all the animals was investigated. The experimental results were subjected to statistical analysis by Student's method.

EXPERIMENTAL RESULTS

After a single injection of myleran in a dose of 10 mg/kg followed by four injections of SSC during a period of 2.5 weeks the rats developed leukopenia and a temporary decrease in the platelet count, but no change in the number of erythrocytes (Fig. 1). The greatest decrease in the leukocyte count of the animals of the control group was observed on the fourth day, down to 58% of normal (7700), after which their number slowly increased to 75% of normal by the 20th day. The leukocyte count of the animals receiving DNA fell by the 4th day to 77% of normal (9600), but after the sixth day it was back to its original values and was

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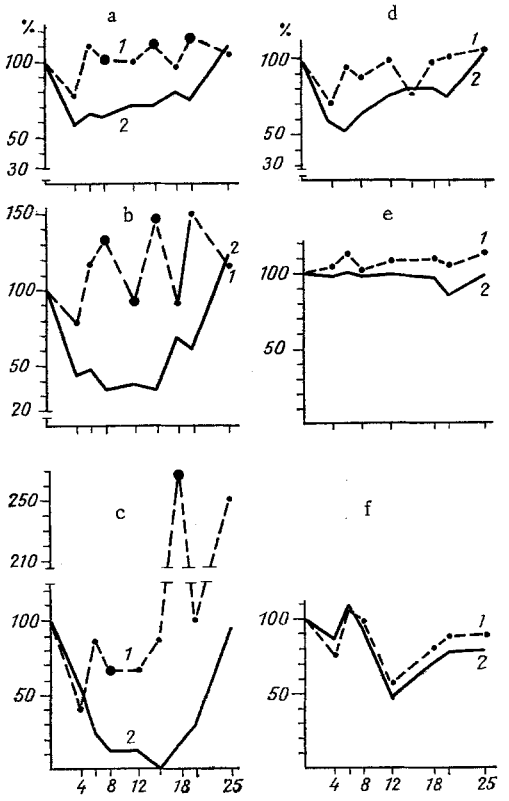

Fig. 1. Dynamics of blood cells in rats after a single dose of 10 mg/kg myleran and four injections each of 2 mg DNA (1) or of SSC (2): a) leukocytes; b) neutrophils; c) stab neutrophils; d) lymphocytes; e) erythrocytes; f) platelets. Abscissa, days after beginning of myleran administration; ordinate, number of blood cells (in % of initial value). Large dots denote values significantly ($P < 0.05$) different from the control.

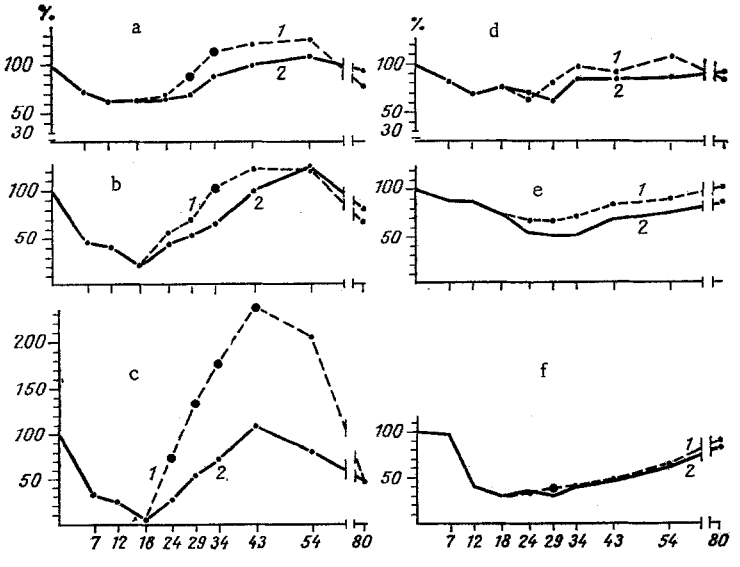

Fig. 2. Dynamics of blood cells in rats after course of administration of 25 mg/kg myleran and five injections each of 2 mg DNA (1) or of SSC (2). Legend as in Fig. 1.

35-40% higher ($P < 0.02$) than in the rats of the control group. The neutrophil count in the untreated animals by the 24th day was reduced to 45% of normal, after which (8th-15th days) it remained between 34 and 38%, compared with 80% in the treated rats on the fourth day, and 92-130% of normal after the sixth day ($P < 0.01$). Changes in the number of stab neutrophils during the 1st day were similar in the untreated and treated animals: It fell by the fourth day to 40-50% of normal. A further decrease in their number between the eighth and 15th days to 0-12% was observed only in the untreated animals, whereas in the treated rats their number was maintained at between 65 and 85% of normal ($P < 0.01$). The lymphocyte count of the untreated rats fell to 54% of normal by the fourth day and gradually returned to normal by the 25th day. Differences between the numbers of these cells in the treated and untreated animals on the sixth to 12th day amounted to 23-37%.

In rats receiving 25 mg/kg myleran over a period of 18 days, leukopenia, anemia, and prolonged thrombocytopenia were observed. By the end of the course of myleran the leukocyte count of the animals was established at the level of 63% (8100) and the neutrophil count at 25% of the initial value (Fig. 2). The leukocyte count of the untreated rats was restored after 10 days, and in the treated rats 5 days sooner. The initial level was reached by the 25 and 15th days, respectively. The higher (by 18-26%) leukocyte count in the treated rats in the period from the 10th to the 35th days was due mainly to neutrophils, the total number of which was 38-23% higher, and the number of stab cells 100-130% higher than in the untreated animals. The erythrocyte count, which fell to 74% toward the beginning of treatment, continued to decrease and in the period from the fifth to the 15th days it was 50% in the untreated animals and 65-70% of normal in the treated animals. The platelet count fell to 28% and was maintained at between 33 and 45% during the next 3 weeks in both the experimental and the control rats.

In both groups 60% of rats survived. Death took place against a background of moderate leukopenia, continuing thrombocytopenia, and increasing anemia. The mean duration of survival of the untreated rats which died was 26 days compared with 33.4 days for the treated rats. The weight of the rats receiving DNA was on average 10-15% greater than in the controls at all times of investigation.

After administration of DNA to rats receiving myleran the duration and depth of the leukopenia were thus reduced, mainly on account of the more rapid recovery of the neutrophil count. Myleran is known to reduce the number of proliferating myelokaryocytes [5, 7, 8] and to inhibit growth of colony-forming units [6, 11]. The prevention of leukopenia induced by myleran, or the reduction in its severity by DNA observed in this experiment could perhaps be attributable to potentiation by DNA of proliferation and maturation of myelokaryocytes [4], and also to proliferation and differentiation of hematopoietic stem cells by DNA [1].*

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