Synergistic Action of Vincristine and Adriamycin in the Treatment of Experimental Rat Leukemia L5222

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ABSTRACT

The therapeutic effect of different ratios of a combination of vincristine and Adriamycin was compared to monotherapy with both substances in advanced rat leukemia L5222. The combination therapy proved to be synergistic.

In the upper dose range, no additive toxicity was observed. The combination of 25% vincristine plus 75% Adriamycin effected the best results.

In a clinically relevant dose range, the superiority of this ratio was observed independent of the application sequence of the two substances and independent of the time interval between the applications within an 11-hr investigation period.

INTRODUCTION

The combination of VCR with ADR is used successfully in the clinic, both for treatment of a wide spectrum of solid tumors (1) and for treatment of hematological neoplasias (7).

A therapeutic synergism of these 2 substances found in the L1210 mouse leukemia system (3) was also confirmed on the P388 mouse leukemia, as well as on the advanced C3H mammary adenocarcinoma and on the Ridgway osteogenic sarcoma in mice (8).

The present investigation deals with the question of whether a therapeutic synergism of this combination can be shown in advanced rat leukemia L5222 and whether the effect of the combination depends on the application sequence or on the period of time between the applications of the 2 drugs.

MATERIALS AND METHODS

Animals and Tumor. The investigations were carried out on 6-week-old female BD IX rats bred in our own laboratory. The growth behavior, proliferation kinetics, and sensitivity to chemotherapy of L5222 leukemia have been described (4, 5, 9). Following cardiac puncture and suspension of the leukemia cells in 0.9% NaCl solution, 3 x 10⁶ cells in 1 ml were implanted i.p. into the receivers.

Drugs. VCR (Vincristin-Lilly) was kindly supplied by Eli Lilly GmbH, Giessen, Federal Republic of Germany; ADR (Adriblastin) was supplied by Deutsche Farmitalia GmbH, Freiburg, Federal Republic of Germany. VCR was injected i.p. in a 0.02% solution in water. ADR was administered i.v. in a 0.1% solution in 0.9% NaCl solution.

RESULTS

Chart 2 shows the median survival time effected by increasing doses with constant ratios of the drugs. After application of VCR (1 mg/kg) or ADR (10 mg/kg), maximum median survival times of 16 and 23.5 days were observed, respectively. VCR (1.5 mg/kg) and ADR (15 mg/kg) were toxic, which was evident from the decrease in the median survival time.

For the combinations, a further (sixth) dosage group had to be added in order to determine the optimum dose, since no additive toxicity was observed. The maximum median survival time achieved by the combination 25% VCR plus 75% ADR was higher than the maximum median survival time achieved by the other combinations or by the monotherapy.

Chart 3 shows a comparison of the median survival times of the experimental groups which are connected by Broken Line I to V in Chart 1; these groups received an equal combined treatment level with varying ratios of the drugs. In principle, these plots contain the same information as Chart 2; however, they underline distinctly the therapeutic superiority of the combination in the lower dose range, which is relevant for the clinic. In the higher dose range, on the other hand, the combination therapy is superior to the monotherapy because of the lack of additive toxicity.

Chart 4 gives a comparison of the results of 6 experimental arrangements. The doses that are connected by Broken Line II in Chart 1 were chosen to investigate the influence...
of the application sequence and of the time interval between the injections on the therapeutic effect.

It becomes evident that the combination of VCR with ADR is superior to monotherapy with these substances, independent of the application sequence within an investigation period of 11 hr. In all experimental arrangements, the combination of 25% VCR plus 75% ADR was superior.

DISCUSSION

The results presented in Chart 2 demonstrate that the maximum median survival time after treatment with the combination 50% VCR plus 50% ADR or 25% VCR plus 75% ADR exceeds the maximum median survival time after treatment with the combination 75% VCR + 25% ADR or with VCR or ADR alone. This increase of the maximum median survival time is a result of the lack of additive toxicity of the substances; if there had been additive toxicity the optimum doses of the combinations would have been toxic. Comparable results regarding the lack of additive toxicity of the combination of VCR and ADR in the therapy of the C3H mammary adenocarcinoma in C57BL/6 × C3H F₁ mice are available; here approximately 70% of the 10%
lethal dose of each drug could be used simultaneously without exceeding the 10% lethal dose in combination.2

In a lower, clinically relevant dose range, a clear therapeutic superiority of the combinations 50% VCR plus 50% ADR and 25% VCR plus 75% ADR to the monotherapy is demonstrated by the profile of the curves in Chart 2. Integration of the surface areas between the curves of Chart 2 and the line of survival time of untreated controls results in surface proportions of 1, 1.9, 3.2, 3.6, and 2.2 for the ratios of 100% VCR, 75% VCR plus 25% ADR, 50% VCR plus 50% ADR, 25% VCR plus 75% ADR, and 100% ADR, respectively. This result, together with the finding that the maximum median survival time of 2 combinations exceeds the maximum median survival time of the monotherapy, gives evidence of a synergistic action.

The results presented in Chart 4 show the superiority of combination therapy against monotherapy, independent of the application sequence and of the time interval between the applications within the investigation period. The best results were achieved with the combination 25% VCR plus 75% ADR in the sequences: ADR, VCR (5-hr interval); VCR, ADR (0-hr interval); and VCR, ADR (6-hr interval). The median survival times achieved exceeded the survival times after monotherapy by about 10 days. As we demonstrated in an earlier experiment on the L5222 model, an increase in survival time of 10 days corresponds to an approximately log 7-higher tumor cell kill (2).

Of the doses tested, the combination of VCR (0.11 mg/kg) + ADR (3.33 mg/kg) achieved the most convincing results in the lower dose range (Chart 4); these results were even comparable to the effect of VCR (0.17 mg/kg) + ADR (5.0 mg/kg) (Chart 2). After conversion to terms of surface area (mg/sq m), VCR (0.11 mg/kg) + ADR (3.33 mg/kg) corresponds to VCR (0.6 mg/sq m) + ADR (20 mg/sq m). These doses lie within the dose range used in the clinics.

REFERENCES

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