Phase I study with 4'-deoxydoxorubicin

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Summary

4'-Deoxydoxorubicin (dxDx), a new doxorubicin analogue, was administered intravenously on a 3-week schedule to 73 patients affected by advanced malignant neoplasms. Sixty-five patients, treated with eight dose levels ranging from 10 to 45 mg/m², were evaluable. The dose-limiting toxicity was myelosuppression, mainly leukopenia. About one third of the patients complained of vomiting which was almost always mild. Minimal hair loss was also documented in about 40% of patients. No hepatic or renal toxicity was observed. Transient and aspecific electrocardiographic changes were recorded in 6% of patients after 1 h and in 3% after 24 h from drug injection. Left ventricular ejection fraction was decreased in two patients after a cumulative dose of 90 mg/m². One patient died with cardiorespiratory insufficiency and his initial cardiovascular disease might have been aggravated by dxDx. No changes in myocardial function parameters were documented in 18 patients who reached higher cumulative doses, i.e. ≥ 100 mg/m² and ≥ 200 mg/m². The highest total dose administered in this study was 340 mg/m². Therapeutic activity was observed with doses ranging from 25 to 45 mg/m². Partial response was documented in pancreatic, colon, anal and breast carcinomas as well as in non-Hodgkin's lymphoma. Minor response was observed in prostatic, thyroid, and renal carcinomas as well as in chronic lymphocytic leukemia. The maximum tolerated dose was assessed to be between 40 and 45 mg/m². A Phase II trial is ongoing utilizing the dose of 35 mg/m² every 3 weeks.

Introduction

4'-Deoxydoxorubicin (dxDx; IMI-58; NSC 267469) is a new doxorubicin (Dx) analogue characterized by lack of the hydroxyl group in position 4' of the aminosugar (Fig. 1) (1). The empiric formula is C₂₇ H₂₉ NO₁₀. HCl and the molecular weight is 563.98.

The compound intercalates into DNA in the same way as Dx. The lack of the hydroxyl group enhances the basicity and therefore the pH of the drug. The modified polarity could explain the slightly higher biological activity of dxDx on DNA polymerase compared to Dx, even though the two compounds had similar inhibitory effects on RNA polymerase (2). dxDx showed superior activity to Dx on Hela cell cloning efficiency after 8 h of exposure and, according to the higher partition coefficient due to increased lipid solubility, it was taken up in a comparative greater amount by L1210 leukemic cells (3).

dxDx has been compared with Dx regarding potency, toxicity, and antitumor activity in mice treated with different schedules (4). The analogue was 1.5 to 2 times more potent and more toxic than Dx, and exerted antitumor activity in several experimental tumors such as P388 and L1210 ascitic leukemias as well as Gross leukemia. In solid murine tumors, dxDx was as active as Dx against mammary carcinoma and MS-2 sarcoma, slightly

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less active against B16 melanoma, and more effective against colon 26 and 38 adenocarcinomas (4). Of particular interest was the reported activity of dxDx against human colon carcinoma, a neoplasm commonly resistant to Dx, xenografted into nude mice. No activity, however, was detected in rectal carcinoma (5, 6, 7). Antitumor effect was also observed in a variety of human neoplasms utilizing the tumor stem cell assay (8).

In animal models dxDx failed to show significant acute and chronic toxicity. At the highest dose tested, the analogue produced only minimal lesions in a small percentage of mice and was not cardiotoxic at lower doses. Rabbits treated with dxDx showed no myocardial lesions (3).

The pharmacokinetics of dxDx has been determined by total fluorimetry in tissue extracts. This analogue reached the same tissue levels as Dx in all organs tested except spleen and lung where comparatively higher peaks were detected (9). In the neoplastic tissue the analogue reached higher concentrations than Dx, as shown by a comparison of the areas under the curve, up to 72 h following administration, and this finding may be correlated with its higher potency. In general, dxDx appears to be eliminated more rapidly than Dx. The faster clearance from the heart has been advocated as one of the reasons for the lower cardiotoxicity of the new analogue (9).

The observed activity in a tumor commonly resistant to Dx, such as colon carcinoma, and the nearly complete lack of cardiotoxicity in mice and rabbits has made this new analogue particularly attractive for a Phase I clinical trial.

Patients and methods

Between January 1982 and July 1983, 73 consecutive patients were treated with dxDx in the Division of Medical Oncology of the Istituto Nazionale Tumori, Milan.

Patient selection

Patients with clinically and histologically documented advanced malignant neoplasms, resistant or poorly responsive to standard drug treatments, were eligible for this Phase I trial. Before administering dxDx, patients had to recover completely from major toxic effects induced by prior therapy. Criteria for exclusion were as follows: life expectancy less than two months, performance status $\leq 50$ (Karnofsky scale), age greater than 75 years, white blood cell count (WBC) $< 4000/\text{mm}^3$, platelet count (PLT) $< 100,000/\text{mm}^3$, serum creatinine and bilirubin levels $> 1.5 \text{mg}\%$, history of congestive heart failure, symptomatic cardiovascular disease or arrhythmia. In patients receiving single doses $> 25 \text{mg}/\text{m}^2$, previous treatment with Dx had not to exceed the cumulative dose of 350 mg/m$^2$. The great majority of patients were treated on ambulatory basis. The study was approved in advance by the Institute’s Committee on Clinical Investigation and all patients were informed that dxDx represented a new experimental analogue.

Drug administration

The drug was supplied by Farmitalia Carlo Erba, Milan, Italy, in 5 mg vials of red powder for intravenous (i.v.) administration. It was reconstituted with distilled water at the concentration of 2 mg/ml and administered by i.v. bolus injection every 3 weeks or following full bone marrow recovery.

The starting dose level was 10 mg/m$^2$ corre-