Clinical evaluation of 4’-epi-doxorubicin in advanced solid tumors

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Summary

A Phase II clinical evaluation of 4’-epi-doxorubicin has been carried out in 100 patients with various types of solid tumors. Hematopoietic toxicity was dose-limiting but reversible and of mild to moderate degree. Other acute toxic manifestations such as vomiting and alopecia were qualitatively similar to those usually reported for doxorubicin, but lower in frequency and less severe. A number of responding patients received cumulative doses of 4’-epi-doxorubicin in excess of 500 mg/m². One patient manifested reversible clinical congestive heart failure at cumulative dose of 1,080 mg/m². Therapeutic activity has been observed in breast carcinoma, in rectal carcinoma and in melanoma. In chemoresistant tumors as rectal cancer and melanoma 4’-epi-doxorubicin deserves further study.

Introduction

Doxorubicin (DX) is one of the most useful anticancer agents; it has major therapeutic activity against breast cancer, sarcomas, ovarian cancer, leukemias and malignant lymphomas (1). However, its usefulness is limited by potential toxicities such as cardiotoxicity, myelosuppression, alopecia and nausea and vomiting.

New analogues of doxorubicin have been developed in the hope of obtaining agents endowed with a broader spectrum of antitumor activity, lessened cardiac toxicity and a better therapeutic index. 4’-Epi-doxorubicin (4’-epi-DX) is among the first of the new analogues to be currently under intensive clinical investigation both as a single agent and in combination chemotherapy. 4’-Epi-DX is an epimer of DX having a different configuration of the 4’-hydroxyl group on the aminosugar moiety. This yielded a compound which was therapeutically comparable to DX in murine tumor systems but less toxic than DX in acute and chronic toxicity tests in animals, including cardiotoxicity (2–4).

Phase I clinical studies of 4’-epi-DX (5, 6) showed that myelosuppression was the dose-limiting acute toxic effect; antitumor activity in Phase I and early Phase II were observed in patients with breast cancer, malignant lymphomas, colorectal cancer, renal cancer, and melanoma (6, 7). A dosage of 70 to 90 mg/m² at 21 days intervals was proposed as appropriate for further Phase II evaluation of 4’-epi-DX.

On the basis of these interesting premises we have activated a Phase II evaluation of 4’-epi-DX in various solid tumors with particular regard to those considered chemoresistant as colon and rectum cancer, malignant melanoma and renal cancer.

Patients and methods

One hundred and fourteen patients were entered into a Phase II study of 4’-epi-DX. 63 males and 51...
females with a median age of 59 years (range 20–70 years). Of these 114 patients, four were judged not evaluable for rapid progression of the disease, two refused further therapy and eight were lost to the follow-up before the third dose. These eight patients are partially evaluable for toxicity but not for response. Of the 100 fully evaluable cases, 70 were previously treated with chemotherapy (44 of these 70 did not receive previous doxorubicin), hormonal therapy (12 patients) and radiochemotherapy (four patients). Thirty patients had received no prior chemotherapy.

Eligibility requirements included: histologic confirmation of metastatic malignancy, which had become refractory to conventional treatment or for which there was no therapy of proven clinical benefit, measurable and/or evaluable disease, an estimated survival of at least eight weeks, a performance status ≥ 50 (Karnofsky scale) and tests for hematologic, renal and hepatic functions within normal limits. No patient had received chemotherapy and/or radiotherapy within the preceding four weeks. Patients with previous history of cardiovascular disease as well as those with previous mediastinal radiotherapy > 40 Gy were not considered eligible.

Pretreatment evaluation consisted of a complete medical history, and physical examination. Laboratory evaluation included complete hemogram, blood sugar and urea nitrogen, serum creatinine, uric acid, bilirubin, alkaline phosphatase, gamma GT, SGOT, SGPT, total protein and electrolytes. Chest X-ray was obtained in all patients. Additional radiologic and histologic studies were performed only when indicated by specific clinical situations. Cardiologic evaluation consisted of the recording of arterial blood pressure, pulse rate, electrocardiogram before each course of therapy, while left ventricular systolic times (PEP, LVET, PEP/LVET) and M-mode echocardiography were recorded in basal conditions and before courses 1, 4, 6, and thereafter every three courses and at the end of each patient trial. In some patients the drug effect on the Left Ventricular Ejection Fraction (LVEF) has been assessed by means of gated blood pool radionuclide angiography scans of the heart.

The drug response criteria were defined as follows: complete remission (CR): disappearance of all signs and symptoms of neoplastic disease for a minimum of one month; partial remission (PR): a > 50% reduction of all measurable neoplastic lesions for at least one month; minor remission (MR): an objective regression > 25% < 50% in tumor measurements; no change (NC): stabilization of measurable and/or evaluable lesions, without appearance of new lesions for at least eight weeks.

4'-epi-DX was supplied by Farmitalia Carlo Erba, Milan, Italy, as a red powder in 10 mg and 50 mg vials. The drug was reconstituted with distilled water and administered by i.v. infusion (60 min) in 250 ml of normal saline every three weeks or upon recovery from myelosuppression. Therapy was discontinued if disease progression became evident or in case of cardiotoxicity. In responding patients the treatment was continued until progressive disease and/or instrumental and clinical evidence of cardiac toxicity. The doses utilized have been of 75 mg/m² i.v. (66 patients) and 90 mg/m² i.v. (34 patients) with an every-three-weeks schedule. The median cumulative dose of 4'-epi-DX through 473 courses was of 380 mg/m² (range 75–1,080 mg/m²). Eighteen patients received a cumulative dose of > 500 mg/m² (range 525–1,080 mg/m²).

Results

Toxicity

The adverse effects observed with 4'-epi-DX are summarized in Table 1. Myelosuppression has been observed in 112 courses out of 473 courses evaluable for toxicity. Leukopenia was severe only in three patients, and complete return to normal counts was observed by the third week in almost all instances. Thrombocytopenia was observed in 5% of the courses. Non-hematologic toxic effects consisted in alopecia observed in 70% of the patients, nausea and vomiting in less than half of all patients, stomatitis in 20%, diarrhea in 13% and chemical phlebitis in 4% of the patients. No renal or hepatic toxicity was observed.

Acute cardiac toxicity of 4'-epi-DX consisted in