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Liposome encapsulated daunorubicin (daunoxome) for acute leukemia

Daunoxome (DNX, Nexstar) was given, as a single agent, to 11 patients with very poor-risk acute leukemia. Pharmacokinetic data were also obtained from 9 of the 11 cases. This small pilot study show that the toxic profile of this liposomal-encapsulated anthracycline is low.

Sir,

Daunoxome (DNX, Nexstar) is a preparation of daunorubicin (DNR) with remarkable physical stability that is encapsulated into small liposomes and is registered for the treatment of AIDS-related Kaposi's sarcoma.[1,2] Since *in vitro* studies have shown that DNX can be at least as effective as free DNR against leukemic cells[3-5] and since DNX is likely to be less toxic than free DNR, we planned a systematic study of DNX in the treatment of acute leukemia. The first part of the study was accomplished by evaluating the effects of DNX alone in 11 patients with very poor-risk acute leukemia (2 cases of advanced blastic phase of chronic myeloid leukemia, 2 cases of acute lymphocytic leukemia (ALL) in 2nd relapse, and 7 cases of ANLL in 2nd or subsequent relapse or primary refractory). The age range of the patients was 39 to 71 years, mean 60±9, median 58.

DNX was given alone, as a single agent, in three doses of 60 mg/m^2 each (days 1, 3 and 5). The infusion was given through a central venous catheter and lasted 1 hour. A complete remission (CR) was obtained in the 2 cases of ALL; one case relapsed after 4 months of unmaintained CR and the other died in CR of a Gram negative septicemia. A partial response with a marked and stable regression of splenomegaly was obtained in the two cases of CML in blastic phase. Both patients were alive 6 and 12 months after treatment. The 7 cases of ANLL failed to achieve CR. Fever developed in 8 of 11 cases. In 4 of 8 cases, the etiology of the fever was bacterial, Gram positive bacteremia in 2 cases, Gram positive and Gram negative bacteremia in 1 case, and fatal Gram negative septicemia in 1 case (after achieving CR). Hospital stay was 15 to 45 days (median 20, range 15 to 45). Blood transfusion support included red cells (median 12 units, range 0 to 25) and platelets (median 3 units, range 0 to 7). Oral mucositis, intestinal toxicity and liver toxicity were not seen. Anti-emetic medications (ondansetron, tropisetron or granisetron) were used prophylactically in 3 cases, but no patient complained of nausea or vomiting.

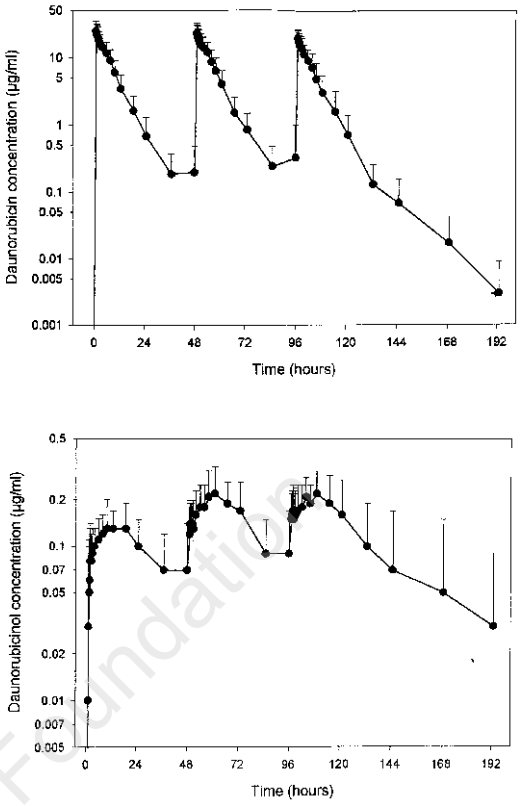

Figure 1. Mean (SD) serum daunorubicin and daunorubicinol concentrations–versus–time profiles following 1-hour i.v. infusion of daunoxome (60 mg/m^2, days 1, 3 and 5).

Pharmacokinetic data were obtained from 9 of the 11 cases by high pressure liquid chromatography. Figure 1 shows plasma concentrations of DNR and its main metabolite, daunorubicinol. The half-life of DNR was 4.65±1.09 hours, with C^{max} ranging between 20 and 25 µg/mL and C^{min} ranging between 0.1 and 0.2 µg/mL. The area-under-the-curve was 472 ±214 µg/mL/h for DNR and 18±8 µg/mL/h for daunorubicinol. All these values are more than a hundred fold higher than those expected with free DNR.[6]

This small pilot trial of DNX alone in patients with very poor-risk leukemia has shown that the toxic profile of this liposomal-encapsulated anthracycline is low, suggesting that it is worth testing higher doses of DNX alone or in combination with other drugs in the treatment of acute leukemia.

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Usefulness of the prognostic score for advanced Hodgkin's disease in patients with human immunodeficiency virus-associated Hodgkin's lymphoma

Prognosis of Hodgkin's disease (HD) in HIV-infected patients has not been extensively studied. The *International Prognostic Factors Project on Advanced Hodgkin's Disease* (IPFPAHD) score has been applied in a series of 12 patients with HIV-related HD in advanced stages treated with combination chemotherapy. The IPFPAHD scores were 5 (4 cases), 4 (1), 3 (6) and 2 (1). Median overall survival for patients with score ≥4 was 3.5 months vs 38 months for patients with scores 2-3 (p=0.01). All patients with score 5 died. These results indicate that IPFPAHD score is also useful for predicting the outcome of advanced HD in HIV-infected patients.

Sir,

The prognosis of Hodgkin's disease (HD) in advanced stages is still poor.[1,2] In 1998 the *International Prognostic Factors Project on Advanced Hodgkin's Disease* (IPFPAHD) developed a score to assess the prognosis of patients with advanced HD .[3] The variables included in this score were: serum albumin < 40 g/L, Hb < 105 g/L, male sex, age ≥45 yr, stage IV, WBC count $\geq 15\times10^9$/L and lymphocyte count $< 0.6\times10^9$/L or < 8% of differential count. Patients with human immunodeficiency virus (HIV) infection are usually excluded from prognostic scores in both HD and non-Hodgkin's lymphomas (NHL) because of their poor prognosis. Since prognosis in HIV-associated lymphomas has improved in recent years, we have evaluated the usefulness of the IPFPAHD score in HIV-associated HD.

Table 1. Main prognostic variables of patients with advanced HD and HIV infection.

Pt	Age (yr)	Gender	Stage	Hb (g/L)	WBC ($x10^9$/L)	Lymph. ($x10^9$/L)	Serum albumin	Score IPFPAHD	OS (mo)
1	22	M	IVB	66	1.01	0.16	24	5	0.5
2	28	M	IVB	68	2.0	0.1	26	5	9
3	32	M	IIIB	119	21.0	2.8	35	3	15
4	32	M	IIB	91	5.2	1.3	25	3	37
5	59	M	IB	108	4.1	1.9	40	2	8+
6	32	M	IVB	93	0.6	0.25	27	5	3
7	24	M	IVA	126	7.2	1.2	34	3	36+
8	28	M	IVB	113	4.5	0.2	31	4	29+
9	28	M	IVB	110	5.8	1.3	25	3	36
10	36	F	IVB	85	3.6	0.8	26	3	39+
11	36	M	IVB	110	4.5	1.3	31	3	15+
12	35	M	IVB	100	2.7	0.3	25	5	3

M: male; F: female; OS: overall survival; IPFPAHD: International Prognostic Factors Project on Advanced Hodgkin's Disease.

From 1990 to 1999, 15 cases of HIV-associated HD were diagnosed in a single center in a cohort of 1,700 patients with HIV infection (prevalence 0.88%). The main risk behaviors for HIV infections were intravenous drug abuse (6 cases), heterosexual promiscuity (5) and homosexuality (4). Four cases had a previous diagnosis of AIDS. Histologic subtypes were lymphocyte depletion (6 cases), mixed cellularity (6) and nodular sclerosis (3). Extranodal disease was present in 10 cases (5 in bone marrow, 2 in liver and 3 in liver and bone marrow). Mean (±SD) CD4 lymphocyte count was 101×10^9/L (±86) (range 10-291).

No treatment was given to 1 patient, 13 received combination chemotherapy (COPP 3, COPP/ABV 8, ABVD 2) and the remaining one was treated with mantle radiotherapy. Complete response was observed in 7 of the 14 evaluable cases (50%), and relapse occurred in two of them. At the time of writing 9 patients have died (7 from progression of HD and 2 from opportunistic infections). Median overall survival (OS) for the whole series was 37 months. Twelve patients had advanced HD (stages III or IV in 10,stage IB with bulky mediastinal mass in one and stage IIB in another) (Table 1). The IPFPAHD scores were 5 (4 cases), 4 (1), 3 (6) and 2 (1). Median overall survival (OS) for patients with score ≥4 was 3.5 months vs 38 months for patients with scores 2-3 (p=0.01). All patients with score 5 died.

Unlike immunocompetent individuals, HIV-infected patients have high histologic grade HD and advanced stages,[4-7] as can be observed in our series. Since we recently observed that the International Prognostic Index (IPI) is useful for prognosis assessment in AIDS-associated NHL,[8] we have evaluated the usefulness of the IPFPAHD score in the assessment of prognosis of