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TENTATIVE DOSE-MONITORING OF DOXORUBICIN IN LYMPHOMA PATIENTS

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We have investigated the feasibility of individual dose-monitoring of doxorubicin in lymphoma patients. The purpose was to overcome the large variability of the early-phase kinetic parameters of the drug. We have used a test-dose and calculated for 32 patients a therapeutic dose which could allow us to obtain a predetermined early drug exposure. Such a predetermined drug exposure was obtained in 24 patients of the study. Important variations of the early clearance occurred in 8 patients.

Key words: **Doxorubicin, Lymphoma, Pharmacokinetics, Dose-monitoring.**

INTRODUCTION

For several years, doxorubicin has been widely used in the treatment of hematologic malignancies and solid tumors. The efficacy of a doxorubicin-containing regimen is generally important[1] and it has been demonstrated that the response is dependent on the dose administered in several types of tumors, especially soft-tissue sarcomas and breast carcinoma.[1] By studying the pharmacokinetic parameters of doxorubicin in locally advanced breast cancer patients, we demonstrated a significant correlation between an early phase parameter (A) and the rapidity of tumor response.[2]

In view of the large variability of the kinetic parameters of doxorubicin,[2–4] it could be of interest to try to inject into patients an amount of drug allowing an optimal drug exposure. The calculation of an optimal therapeutic dose generally depends on the results provided by a test-dose.[5] In this study, our aim was to evaluate the feasibility of the use of a test-dose to calculate a therapeutic dose designed to obtain a predetermined value of the early-phase drug exposure to doxorubicin. We have conducted this study in patients suffering from a Hodgkin's disease or a non-Hodgkin's lymphoma for several reasons: these malignancies are highly sensitive to doxorubicin; the absence of dose-dependence of the response in a wide range of doses (25–75 mg m^{-2})[1] allowed us, from an ethical point of view, to give very different doses in similar patients without losing the efficacy of the treatment. Moreover, we had already developed a study on the pharmacokinetics of doxorubicin in non-Hodgkin's lymphoma patients.[6] Finally, we had conducted a study on the time- and dose-dependence of the early phase kinetics of doxorubicin in non-Hodgkin's lymphoma patients.[7] This study had revealed that the kinetics of doxorubicin were not time-dependent over a 6 h interval and that a test-dose of 10 mg was only slightly dose-dependent, the mean early clearance being increased by 16% between such a test-dose and a therapeutic dose of 40–80 mg. Therefore, our present study was conducted with test-doses of 10 mg, given in the morning; the pharmacokinetics parameters were immediately evaluated and the therapeutic dose given in the afternoon. This study reveals that it is very difficult to overcome the large variability of the parameters of doxorubicin kinetics and that a predetermined early-phase drug exposure could be reached only in 75% of the patients subjected to the study.

PATIENTS AND METHODS

Patients

Thirty-two patients entered the study. Sixteen had a non-Hodgkin's lymphoma, and 16 a Hodgkin's disease. Diagnoses were assessed by histological examination. The ages of the patients ranged from 16 to 71; none of them had signs of hepatic or renal dysfunction. The main clinical features are presented in Table 1. Non-Hodgkin's lymphoma patients receive in our Institute[11] a regimen contain-

Table 1. Clinical features of the patients entering the study

Patient	Sex and age	Disease[a]	Stage[b]
1	M 34	HD, 3	III A
2	M 30	HD, 2	II A
3	M 33	HD, 2	IV B
4	F 28	HD, 2	II A
5	M 41	HD, 2	III A
6	M 70	HD, 3	I A
7	F 63	NHL, IB	III A
8	F 32	HD, 2	I A
9	M 38	NHL, LB	IV B
10	M 29	HD, uncl	II A
11	M 20	HD, 2	I A
12	M 22	HD, uncl	II A
13	M 71	HD, 3	I A
14	F 41	HD, 2	I A
15	M 56	NHL, LB	IV B
16	F 26	HD, 2	II A
17	F 16	NHL, LB	IV A
18	M 61	NHL, LC	II A
19	M 55	HD, 3	I A
20	M 55	NHL, LC	IV A
21	M 25	NHL, LB	IV A
22	F 45	NHL, CBCC	IV A
23	M 16	NHL, LB	III A
24	F 70	NHL, CB	I A
25	F 43	NHL, CC	III A
26	M 27	NNL, CBCC	III A
27	M 48	HD, 1	I A
28	M 38	NHL, LB	IV A
29	F 69	NHL, CBCC	I A
30	M 31	HD, 2	III B
31	M 49	NHL, LP	III A
32	F 44	NHL, CBCC	III A

[a]Abbreviations as follows: HD, Hodgkin's disease — types 1–4 according to Rappaport *et al.*[8], uncl: unclassifiable; NHL, Non-Hodgkin's lymphoma — types according to Lennert[9], IB: immunoblastic; LB: lymphoblastic; CBCC: centroblasto-centrocytic; LC: lymphocyctic; LP: lymphoplasmocytic; CC: centrocytic.
[b]Staging for Hodgkin's disease and non-Hodgkin's lymphoma according to Carbone *et al.*[10]

ing 35 mg m^{-2} of doxorubicin, cyclophosphamide (400 mg m^{-2}) and vincristine (0.7 mg m^{-2}). The Hodgkin's disease patients entering the study usually receive[12] 25 mg m^{-2} of doxorubicin, 10 mg m^{-2} of bleomycin, 6 mg m^{-2} of vinblastine and 150 mg m^{-2} of dacarbazine.

None of the patients had recieved previous chemotherapy or radiotherapy. For the study, the patients first received doxorubicin exclusively, the remainder of their chemotherapy being injected after the last blood sampling of the afternoon. The doxorubicin dose was fractionated in two parts, 10 mg in the morning and, in the afternoon, a dose calculated from the analysis of blood samples obtained after the first dose. Injections of doxorubicin were given by i.v. bolus over 3 min exactly, in the morning as in the afternoon. Blood samples were taken from the opposite arm into EDTA-containing tubes, at precise selected times close to 3, 6, 9, 12, 15 and 20 min after the end of the injection. The blood was centrifuged and the doxorubicin content of the plasma was immediately analysed.

Analysis of the drug

Extraction and analysis of the drug and its metabolites were performed as already described.[13] Briefly, plasma was run on Sep-pak C18 cartridges, from which the anthracyclines were eluted with an organic solvent. This extract was injected in a Waters high-performance liquid chromatograph, using a Microbondapak-phenyl column and an isocratic solvent mixture of acetonitrile/ammonium formate buffer 32/68, nearly as described by Israel *et al.*[14] Detection was performed by flow spectrofluorometry with a Schoffel SF 970 instrument. Daunorubicin was added in known amounts to the plasma before extraction and was used as an internal standard. All extracts were analysed in duplicate.

Mathematical processing of the data

As already described,[7] the experimental data were plotted on semi-logarithmic graph paper. The first 5 points (3–15 min) were always found to be in alignment, often also with the last one (20 min). A linear regression analysis was performed and provided an intercept Y and a slope α with a coefficient of correlation always higher than 0.99. In order to take into account the duration T of the injecton, we have used the following equation giving the plasma concentration C_t as a function of time t:

$$C_t = \frac{A}{\alpha T} (e^{\alpha T} - 1)\, e^{-\alpha t}, \text{ for } t > T.$$

During the first 15–20 min after injection, it was not necessary to take into account the other phases of the kinetics of the drug, because parameters B and C, which are the analogs of A for the other phases of the kinetics,[2] are 20–200 times smaller than A and can be neglected. The error on the early clearance is smaller than 5% (personal observations), which is of the same order of magnitude as the analytic reproducibility.

The estimation of Y and α allowed us to compute the early exposure to the drug defined as

$$\frac{A}{\alpha} = \frac{YT}{e^{\alpha T} - 1}$$

and the early clearance of the drug defined as the ratio (dose)/(A/α).

Several values of the early-phase drug exposure to be reached were chosen. In previous studies on non-Hodgkin's lymphoma patients,[6,7] a mean value of 550 ng ml^{-1} per h was obtained and was therefore chosen in the present study in most cases. Values of 450 and 600 ng ml^{-1} per h were also tested. In Hodgkin's disease patients, who received a lesser amount of doxorubicin in the usual regimen, the early-phase drug exposure required was set at 450 or 550 ng ml^{-1} per h. The therapeutic dose was obtained by multiplying the test-dose used (10 mg) by the ratio of the drug exposures required and obtained with the test-dose:

$$\text{therapeutic dose} = \text{test-dose} \times \frac{\text{required drug exposure}}{\text{test drug exposure}}.$$

For practical reasons, the value obtained was approximated to the nearest dose divisible by 5.

RESULTS

We present in Table 2 the drug exposures obtained in the patients for the test-dose and for the therapeutic dose. The drug exposures obtained after

Table 2. Early-phase drug exposure obtained in the patients after the test-dose and after the therapeutic dose

Patient	Drug exposure after test-dose of 10 mg (ng ml^{-1} per h)	Conventional dose (mg)	Drug exposure to be reached (ng ml^{-1} per h)	Dose proposed (%)	Drug exposure actually reached after therapeutic dose (ng ml^{-1} per h)	Variation of the early clearance (%)
1	79.9	40	450	55	312	+ 41
2	122	40	450	35	321	+ 32
3	84.3	45	450	50	387	+ 9
4	91.2	35	450	50	388	+ 17
5	84.1	50	450	55	393	+ 18
6	112	40	450	40	398	+ 12
7	92.8	40	450	50	403	+ 15
8	93.6	35	450	50	450	+ 4
9	95.9	40	450	45	454	− 9
10	80.3	50	450	55	467	− 5
11	60.9	50	450	75	497	− 8
12	81.7	40	450	55	499	− 10
13	109.5	50	450	50	519	− 12
14	151	35	550	35	323	+ 64
15	95.4	70	550	55	416	+ 27
16	118	55	550	45	508	+ 2
17	106	50	550	50	516	+ 5
18	99.1	60	550	55	518	+ 5
19	46.2	70	550	120	589	− 6
20	54	70	550	105	644	− 12
21	44.8	70	550	120	748	− 28
22	142	60	600	45	446	+ 43
23	88	55	600	70	465	+ 32
24	104	55	600	60	545	+ 14
25	101	55	600	60	555	+ 9
26	74.2	65	600	80	576	+ 3
27	103	65	600	60	583	+ 6
28	76.9	55	600	80	648	− 5
29	112	50	600	55	682	− 10
30	66.6	65	600	90	684	− 12
31	76.7	65	600	80	702	− 13
32	84.2	60	600	75	775	− 22

the 10 mg test-dose range between 46.2 and 151 ng ml^{-1} per h. In 8 patients, the drug exposure obtained after the therapeutic dose was far from the predetermined value: in these cases, the kinetics were not linear, and an increase of 27–64% of the early clearance could be noticed in 6 cases and a decrease of 22–28% in 2 cases. For the other 24 patients, the required value ± 20% was obtained; that means that the early clearance was unchanged. This drug exposure was obtained in 12 cases by the administration of a dose identical to the conventional dose (± 5 mg); in 11 cases it was obtained by an increase of the therapeutic dose by 10–50 mg. In one case only, the therapeutic dose had to be lowered, as compared to the conventional dose, to obtain the required value.

No relation of the pharmacokinetic data with any of the clinical features listed in Table 1 has been evidenced in this study.

DISCUSSION

Our results confirm the values of the early phase kinetic parameters of doxorubicin in humans we had already obtained in lymphoma patients[6,7] as in breast cancer patients.[2] Our results confirm also that, in most cases, the kinetics of doxorubicin are linear from 10 to 120 mg, and that the early clearance variation is lower than 20%, between the test-dose of 10 mg and the therapeutic dose ranging from 30 to 120 mg, in about 75% of the patients. This linearity however is not preserved in 8 patients, and in 6 of them, a large increase of the clearance is noticed, similar to that observed in our previous study for a therapeutic dose/test-dose ratio of 10 or 8.

The originality of the present study is that the therapeutic dose was calculated after the kinetic parameters had been measured on a test-dose. Under these conditions, the drug exposure reached a required value in 75% of the patients, both for Hodgkin's disease patients and for non-Hodgkin's lymphoma patients. Such a use of a test-dose allows, therefore, a better standardization of the doxorubicin exposure of patients. A better reproducibility of the exposure to a drug may be a useful tool for the comparison of protocols containing different dosages of doxorubicin, because of the large interindividual variation of kinetic parameters. Moreover, it could be of interest to achieve optimal early phase drug exposures in the treatment of doxorubicin dosage-dependent tumors, such as sarcomas or breast cancers,[1] since we have shown how important could be the early phase of doxorubicin kinetics in determining the rapidity of the tumor response.[2] Such a short-term efficacy was not evaluated in this study because of the great heterogeneity of the clinical stages of the patients (tumor size and localization) which hampers reliable evaluation of the tumor response; moreover, the combination of doxorubicin with other highly active drugs prevented us from recording the effect of doxorubicin alone, and a similar evaluation of the other agents included in the combinations is required. Our purpose is now to evaluate the actual benefits of such a pretherapeutic exploration in other series of patients; the use of a test-dose in the monitoring of doxorubicin-containing chemotherapy is a complex and expensive procedure the value of which has to be proved.

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