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Doxorubicin: Effect of Different Schedules on Toxicity and Anti-tumor Efficacy

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Abstract—*The risk of congestive heart failure restricts the clinical use of doxorubicin to cumulative doses of* 450–550 mg/m^2, *when it is given using high-dose rapid intravenous application. As the high peak serum levels which follow rapid administration seem to be correlated with cardiotoxicity, application schedules leading to lower peak serum concentrations have been developed. This paper reviews the influence of those schedules on cardiotoxicity, non-cardiac toxicities, pharmacokinetic data and antineoplastic efficacy. While the reduction of cardiotoxicity by long-term application schedules is well documented, much less can be said about the antitumor effect of those schedules. Controlled studies dealing with this problem are needed. This review provides a base for that purpose.*

INTRODUCTION

DOXORUBICIN toxicity includes manifestations well known from many chemotherapeutic agents, namely myelosuppression, alopecia, mucositis and gastrointestinal upset, as well as local tissue necrosis upon extravasation [1–3]. Additionally, like the other anthracyclines, DOX carries the risk of potentially lethal cardiomyopathy, characterized clinically by biventricular, progressive congestive heart failure (CHF) [4–6]. As the amount of myocardial damage is closely related to the cumulative amount of drug given [4, 7, 8] when 3-weekly bolus injections, as described by Benjamin *et al.* [9], are used, it has been recommended that the cumulative dose should not exceed 450–550 mg/m^2 [4, 7]. Except for promising results with the iron chelator ICRF 187 [10], attempts to lower DOX cardiotoxicity with different medications (such as, for example, *N*-acetylcysteine [11] and vitamin E [12]) have so far not shown a significant cardioprotective effect in humans. A totally different approach to improve the therapeutic index of doxorubicin was found by altering the traditional 3-weekly bolus injection schedule. A critical evaluation of the data published regarding schedule dependence of doxorubicin toxicity and antitumor efficacy seems to be needed to improve the therapeutic utility of this highly effective antineoplastic drug.

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SCHEDULE AND CARDIOTOXICITY

Several studies have been able to demonstrate a reduction of clinically apparent cardiac damage with weekly DOX (Table 1). In the largest reported series, von Hoff *et al.* retrospectively reviewed the charts of several thousand patients who had been treated with different DOX-containing chemotherapy regimens [8]. They found the overall incidence of DOX-induced CHF to be 2.2%, with the highest risk for the standard q 3 week treatment, an intermediate risk for 3 daily doses q 3 weeks ($P = 0.06$), and a significantly reduced risk for the q 1 week schedule ($P = 0.0001$). With all schedules, there was a continuous increase of CHF probability with cumulative DOX dose, rather than an absolute cut-off point. Interestingly, at *post mortem* examination, only 37% of those hearts clinically diagnosed as having DOX-induced cardiomyopathy showed accompanying morphological changes, as did 8% of clinically uninvolved hearts.

In a randomized study, Jain *et al.* could demonstrate a decreased incidence of clinically overt heart failure with weekly as opposed to 4 weekly DOX, and this even though the dose intensity was higher in the q 1 week arm [13]. A non-randomized trial by Torti *et al.* came to similar results [14]. Large groups of patients on weekly DOX with a remarkably low incidence of DOX-related cardiomyopathy have been reported by the Central Oncology Group [16, 17] and the Western Cancer Study Group [18, 19]. Factors other than DOX have been made responsible for most of the few cases of myocardial dysfunction observed in these series. Several authors

Table 1. Clinical cardiotoxicity following bolus injection of doxorubicin: influence of application interval

Author		Pts	Schedule	DOX (mg/m²)	Cumulative dose (mg/m²) mean*	range	CHF (%)
von Hoff	[8]	2230	q 3 wk		240	(13–5047)	2.9
		954	q 1 wk				0.8
Jain	[13]	31	q 4 wk	37.5			6.5
		26	q 1 wk	12.5			0.0
Torti	[14]	98	q 3 wk	60	392		13.3
		27	q 1 wk	20	440		0.0
Borden	[15]	94	q 3 wk	70			1.1†
		89	q 1 wk	15			0.0†
Weiss	[16, 17]	649	q 1 wk	12–18‡		(−≥600)	0.6–1.2
Chlebowski	[18]	305	q 1 wk	15–30‡		(<450)	0.0
		21	q 1 wk	15–30‡		(450–600)	0.0
		10	q 1 wk	15–30‡		(>600)	0.0
Chlebowski	[19]	55	q 1 wk	15–21.75‡	304	(≤870)	0.0
Mattson	[20]	81	q 1 wk	6–12		(−≥750)	0.0
Specenier	[21]	24	q 1 wk	10			0.0
Kessinger	[22]	38	q 1 wk	5–11.5		(10–720)	0.0
Fossa	[23]	22	q 1 wk	11.6§	92.8*	(35–694)	0.0
Frenay	[24]	81	q 1 wk	12	668‖		0.0

Pts = evaluable patients.
*Median.
†Death from CHF.
‡Converted from mg/kg (1 m²/30 kg).
§Converted from absolute dose to standard body surface of 1.73 m².
‖Including previous DOX by bolus administration.
¶Additional previous DOX by bolus administration.
**Not all patients.

have given weekly low ('mini') dose DOX. CHF was not seen even in those patients where the cumulative dose exceeded 750 mg/m² [20–24].

While clinical observation allows for detection of severe cardiac damage, other methods have to be relied upon for quantification of more subtle changes. However, only a few of the reviewed studies have systematically searched for subclinical myocardial dysfunction. Histomorphologically analyzing endomyocardial biopsies according to the grading score for cardiac damage as described by Billingham *et al.* [25], both Valdivieso *et al.* (difference in median scores: $P = 0.01$) [26] and Torti *et al.* (fewer cases of severe damage: $P = 0.002$) [14, 27] were able to demonstrate a significant reduction of cardiotoxicity for q 1 week opposed to q 3 week administration.

Left ventricular ejection fraction (LVEF) measurement has been used as a non-invasive technique for quantification of cardiac function. With DOX q 1 week, a significantly smaller deterioration of stress LVEF in multigated cardiac blood pool scans was seen by Jain *et al.* than with an every 3 week schedule (0/26 vs. 4/31 patients with >0.05 fall from baseline) [13]. Valdivieso *et al.*, however, using m-mode echocardiography, could not show striking differences in LVEF between their two treatment schedules [LVEF median 67.5% (55–87%) with DOX q 1 week; 61% (50–75%) with DOX q 3 week] [26].

Like fractioning a dose (as shown above for weekly instead of 3-weekly applications), prolonging the time allowed for a particular infusion of the drug has been investigated in order to reduce doxorubicin's cardiotoxicity (Tables 2 and 3). So far, a reduction of cardiotoxicity has not been proven for infusions lasting less than 24 h. In addition to a 9.1% incidence of congestive heart failure with 6-h infusions, Speyer *et al.* observed progressive and significant decreases of resting LVEF with increasing cumulative DOX in cardiac blood pool scans [28]. The lack of cardiotoxicity in the study reported by Gercovich *et al.* (10-h infusions) is well explained by the low cumulative amount of DOX administered [29]. The

Table 2. Clinical cardiotoxicity of doxorubicin: influence of length of infusion

Author		Pts	Time (h)	DOX (mg/m^2)	Cumulative dose (mg/m^2) Mean	Range	DOX-induced CHF (%)
Speyer	[28]	33	6	50	408		9.1
Gercovich	[29]	20	10	60–75	135		0.0
Legha	[30]	21	Bolus	60		(500–800)	24
		20	24–48	60		(500–800)	0.0
		21	96	60		(500–800)	0.0
		14	24–48	60		(>800)	14
		34	96	60		(>800)	9
Speyer	[33]	39	24	60–90		(60–675)	0.0
Tannir	[34]	42	48	50		(≤850)	0.0
Feusner	[35]	3	48	40–45		(≤647)	0.0
Ortega	[36]	11	96	60–90		(180–720)	0.0
Neglia	[37]	5	9t	90		(170–720)	0.0
Bowen	[38]	5	120	45–75		(4–6 cs)	0.0

Time = time allowed for doxorubicin infusion (h = hours, d = days, wk = weeks, mo = months); cs = courses; other explanations: see Table 1.

Table 3. Clinical cardiotoxicity following long-term doxorubicin infusion

Author		Pts	Infusion (time)	DOX ($mg/m^2/d$)	Cumulative dose (mg/m^2) Mean	Range	DOX-induced CHF (%)
Lokich	[39]	56	14–60 d	2–5			0.0
Garnick	[40]	14	1–28 wk	1–9	330	(14–956)	0.0
Bode	[41]	11	7–52 d	5–10		(≤1800)‖	0.0
Vogelzang	[42]	13	104 (11–228) d	2–5.5	404‖	(10–1039)‖	7.7
Vogelzang	[43]	17	86 (21–138) d	≥3	202*	(32–877)¶	0.0
Samuels	[44]	17	118 (28–212) d	3–5.5	268*	(105–1097)¶	11.1

Explanations: see Tables 1 and 2.

most convincing data for a reduction of cardiotoxicity with prolongation of infusions have come from the M.D. Anderson Hospital in Houston. In a non-randomized study, Legha *et al.* were able to demonstrate a remarkable reduction of clinical cardiotoxicity with increasing length of infusion, and could substantiate their findings by analyzing endomyocardial biopsies: 24–48-h infusions did not lead to cardiac damage comparable to that of bolus administration at 500–800 mg/m^2 until cumulative doses exceeded 800 mg/m^2, while 96-h infusions were well tolerated even then [30–32].

In addition to these data, several other authors, most of them with small patient series, have observed little cardiotoxicity with infusions lasting 24-h or more [33–38]. No decrease of cardiac function in gated pool scans was seen by Speyer *et al.* [33] and no significant alterations of radionuclide LVEF were observed by Neglia and Woods [37].

Recently, ambulatory infusion pumps and permanently implanted central venous catheters have enabled continuous administration of DOX over periods of time lasting from weeks to several months (Table 3) [39–44]. Little information regarding subclinical cardiac damage has been reported in the papers reviewed. However, the authors agree that in those few patients examined for subclinical damage, the amount was less than expected from a given cumulative dose. In these continuous infusion studies, the cumulative amount of DOX administered to patients via continuous infusion, together with previous doses by standard schedules, often exceeded 1000 mg/m^2, and the amount of clinical cardiotoxicity observed must therefore be regarded

as extremely low. Cases of clinical cardiotoxicity were only observed at cumulative doses well above 550 mg/m² [42, 44].

SCHEDULE AND NON-CARDIAC TOXICITIES

Uncontrolled studies using DOX q 1 week as a single agent found a similar incidence and severity of myelotoxicity as would have been expected from q 3 week schedules [16, 18]. In accordance with these data, the randomized combination chemotherapy study reported by Valdivieso *et al.* demonstrated similar counts of leukocytes as well as platelets for both schedules. However, the absolute neutrophil count was higher in patients on the q 1 week schedule ($P = 0.01$) [26]. The low amount of hematologic toxicity in the q 1 week arm of an ECOG study reported by Borden *et al.* [15] and in several other studies [20–24] is well explained by the low doxorubicin doses used. A tendency towards more mucositis has been noted with q 1 week schedules, nausea and vomiting or alopecia were not significantly altered.

Acute gastrointestinal upset has, however, been markedly reduced by prolongation of DOX infusions, and alopecia may be lessened too. Myelotoxicity has not been convincingly altered [29, 31, 33, 38, 45], and mucositis increases in frequency and severity with increasing length of infusion [31–33, 38, 45]. Accordingly, when DOX is given continually over weeks or months, mucositis becomes the most common dose limiting factor, followed in frequency by myelosuppression, namely granulocytopenia [39–44, 46]. Recommended daily doses for this continuous application schedule are within a close range from 3 to 4 mg/m²/d [39–43]. Catheter and pump complications (such as drug leakage, thrombosis or local infection) pose an additional hazard when prolonged infusions are used.

SCHEDULE AND DRUG LEVELS

It has repeatedly been hypothesized that higher peak serum levels of DOX might be associated with more severe cardiotoxicity [16, 30]. As shown in Table 4, the peak concentration of doxorubicin is

Table 4. Doxorubicin schedule and drug levels

Author		DOX (mg/m²)	Schedule	ng/ml	ng/ml / mg/m²
Speth	[47]	30	Bolus	1447 ± 681	48.2 ± 22.7
Speth	[48]	30	Bolus	1640 ± 470	54.7 ± 15.6
Eksborg	[49]	20.5*	Bolus	>1000†	≥50
Eksborg	[50]	38.9†	Bolus	5251 ± 3345†	135 ± 86
Tidefeld	[51]	11.6‡	Bolus	196	16.9
Erttmann	[52]	15	Bolus	>2000†	133.3
Eksborg	[50]	38.9†	0.75 h	840 ± 128†	21.6 ± 3.3
Eksborg	[50]	38.9†	2 h	398 ± 78†	10.0 ± 2.0
Speth	[48]	30	4 h	176 ± 34	5.9 ± 1.1
Eksborg	[50]	38.9†	4 h	245 ± 155†	6.3 ± 4.0
Raijmakers	[53]	30	4 h	60–80	2.0–2.7
Speyer	[28]	50	6 h	49–65	0.98–1.3
Speth	[48]	30	8 h	85 ± 50	2.8 ± 1.7
Eksborg	[50]	38.9†	8 h	159 ± 23†	4.1 ± 0.59
Eksborg	[50]	38.9†	16 h	86†	2.2
Raijmakers	[53]	30	24 h	20	0.66
Legha	[54]	75*	24 h	140	1.9
Legha	[54]	75*	48 h	80	1.1
Speth	[48]	30	72 h	47 ± 5	1.6 ± 0.17
Speth	[47]	36	96 h	15.8 ± 4.4	0.44 ± 0.12
Legha	[54]	75*	96 h	60	0.80
Riggs	[55]	60	96 h	50 ± 19	0.83 ± 0.32
Sincule	[56]	21–189§	1–13 mo	<0.75–9.9	<0.035–0.060
Garnick	[40]	21–189§	1–28 wk	<0.8–13.0‖	<0.038–0.93

Measured (ng/ml) and dosage adjusted (ng/ml per mg/m² administered) doxorubicin levels. Only results obtained with methods capable of specific doxorubicin detection are reported.

*Median of a reported dose range.

†Calculated from a table or figure in the original paper.

‡Converted from absolute dose to standard body surface of 1.73 m².

§mg/m² per 3 weeks.

‖Measurable DOX in only 2/14 patients.

Table 5. Clinical efficacy following bolus injection of doxorubicin: influence of application interval

Author		Schedule	DOX (mg/m^2)	Other drugs	Breast	Lung	Sarcoma	Lymphoma	Ovary	Colorectal	Other	
Valdivieso	[26]	q 3 wk	60	Ft,C,P	19% (42)							
		q 1 wk	20	Ft,C,P	31% (45)							
Jain	[13]	q 4 wk	37.5	Mi	45% (31)							
		q 1 wk	12.5	Mi	42% (26)							
Borden	[15]	q 3 wk	70	—	16% (92)		16% (92)					
		q 1 wk	15	—	19% (93)		19% (93)					
Weiss	[16]	q 1 wk	12–18‡	—	49% (37)	13% (31)	32% (64)	89% (42)	89% (12)	0% (36)	Kidney	9% (34)
											Melanoma	14% (14)
											Bladder	46% (15)
Weiss	[17]	q 1 wk		MTX,C, FU,V	69% (75)	31% (26)	83% (6)	75% (15)	69% (28)	10% (20)	Endometrium	33% (6)
											Myeloma	100% (2)
Chlebowski	[18]	q 1 wk	15–21.7‡	—	35% (31)	14% (57)	24% (62)	29% (17)	25% (8)	0% (13)	Head and neck	13% (16)
											Bladder	29% (17)
											Diverse	11% (53)
Chlebowski	[19]	q 1 wk	15‡	MTX			12% (16)					
		q 1 wk	18.7–22.5‡	MTX			28% (39)					
Torti	[62]	q 1 wk	20	—							Prostate	16% (25)
Mattson	[20]	q 1 wk	6–12	—	58% (46)	20% (20)		100% (15)				
Specenier	[21]	q 1 wk	10	—	0% (24)							
Kessinger	[22]	q 1 wk	5–11.5‡	C,B**							Diverse	14% (36)
Fossa	[23]	q 1 wk	11.6§	—							Prostate	0% (21)
Frenay	[24]	q 1 wk	12	—	32% (81)							

Reported response rates and number of evaluable patients (in brackets) by tumor type. Explanations: Ft = Ftorafur; C = cylophosphamide; P = *cis*-platinum, Mi = mitoxantrone; MTX = methotrexate; FU = fluorouracil; V = vincristine; B = bleomycin; VBL = vinblastine; D = DTIC; Dex = dexamethasone. Other explanations: see Table 1.

both dose- and schedule-dependent [28, 40, 47–56]. A reduction by several orders of magnitude can be achieved by prolongation of the infusion. However, the total area under the curve (AUC), probably one of the most important pharmacokinetic parameters for antitumor efficacy, does not seem to be compromised by schedule alterations [47, 48, 50].

SCHEDULE AND *IN VITRO* EFFICACY

The time dependence of anthracycline cytotoxicity has been investigated in different *in vitro* models including bone marrow stem cells [53, 57, 58] and hamster ovarial cells [59] as well as in some tumor [59, 60] and leukemia cell lines [57]. As early as 1975, Barranco observed that a fractionated low-dose doxorubicin application technique was more effective at reducing cell survival *in vitro* than a single large dose [61]. Eichholtz-Wirth could clearly show in HeLa S3 cells *in vitro* that under various concentrations the cytostatic effect of doxorubicin was proportional to the product of concentration and incubation time [59]. It has been confirmed by various other *in vitro* studies that long term exposure to low doses of anthracyclines is even more effective than short-term high-dose application leading to an identical concentration × time product [53, 57, 58].

SCHEDULE AND CLINICAL EFFICACY

While the reduction of doxorubicin's cardiotoxicity by schedule alterations has been convincingly demonstrated, much less information regarding the clinical efficacy of these altered schedules is available. Varying histological tumor subtypes and different amounts of pretreatment enhance the difficulties in the interpretation of the response rates compiled in Tables 5 and 6.

Valdivieso *et al.* prospectively randomized bewteen q 1 week and q 3 week application of DOX as part of an FACP (Ftorafur/doxorubicin/cytoxan, *cis*-platinum) chemotherapy for adenosquamous lung cancer. The difference in response rates was not statistically significant [26]. Neither Jain *et al.* [13] nor Borden *et al.* [15] used DOX with equal dose intensity in the arms of their respective studies, so that caution is advised in interpreting their results.

Relatively large series of different tumors treated with weekly DOX as a single agent or as part of a combination chemotherapy have been reported by the Central Oncology Group [16, 17] and the Western Cancer Study Group [18, 19]. Data for endocrine refractory prostate cancer were published by the Northern California Oncology Group [62]. Response rates similar to those known from standard 3 weekly administration were found. The value of weekly low ('mini') dose DOX remains to be ascertained, as the reported response rates show a very wide variation [20–24].

Unfortunately, none of the reports dealing with prolonged DOX infusions of 6–120 h duration is a controlled randomized study with DOX infusion time being the variable (Table 6). Uncontrolled studies dealing with the response of miscellaneous tumors to DOX monotherapy without control groups were presented by several authors [29, 31–33, 38, 45], as was combination therapy including prolonged DOX infusions [28, 30, 34, 36, 63]. The response rates found were felt to be equal to or even slightly higher than those reached with rapid infusion scheules. When interpreting the response data of those studies utilizing continuous infusion of DOX over weeks to months (Table 7), one has to keep in mind that most of the patients had received prior extensive chemotherapy, often including conventional schedule DOX [39, 40–44, 46]. To our knowledge, no prospective and randomized studies comparing the efficacy of conventional and long-term DOX infusions in humans have been published.

Table 6. Clinical efficacy of doxorubicin with varying length of infusion

Author		Infusion (time)	DOX (mg/m^2)	Other drugs	Breast	Lung	Sarcoma	Liver	Other	
Speyer	[28]	6 h	50	FU,C	79% (33)					
Green	[45]	6–24 h	60–90	—		5% (22)				
Gercovich	[29]	10 h	60–75	—					Diverse	30% (20)
Speyer	[33]	24 h	60–90	—	25% (4)	7% (15)			Endometrium	50% (6)
Legha	[31]	24–96 h	60	—	50% (26)					
Tannir	[34]	48 h	50	VBL	43% (42)					
Legha	[30]	96 h	60	V,D,C			58% (36)			
Ortega	[36]	96 h	60–90	p**						
Barlogie	[63]	96 h	36	V,Dex				83% (11)	Multi.myeloma	59% (29)
Bowen	[38]	120 h	45–75	—			33% (3)			

Reported response rates and number of evaluable patients (in parentheses) by tumor type. Explanations: see tables 1 and 5.

Table 7. Clinical efficacy of long-term doxorubicin infusions

Author		Infusion (time)	DOX (mg/m²/d)	Breast	Lung	Sarcoma	Liver	Kidney	Colorectal	Prostate	Other	
Lokich	[39]	14–60 d	2–5	15% (13)	0% (7)	11% (9)	33% (3)			100% (1)	Mesothelioma	33% (3)
											Pancreas	0% (4)
											Gastric	0% (4)
											Diverse	0% (8)
Garnick	[40]	1–28 wk	1–9	33% (3)		0% (4)						
Bode	[41]	7–52 d	5–10			0% (7)					Diverse	50% (4)
Vogelzang	[42]	11–228 d	2–5.5	100% (1)		25% (4)		0% (1)		0% (2)	Parotis	0% (1)
											Bladder	0% (1)
Vogelzang	[43]	32–877 d	≥3					0% (5)	0% (5)		Diverse	25% (12)
Samuels	[44]	28–212 d	3–5.5			22% (17)						
Ballieul	[46]	17–144 d	2.5–6.5	22% (9)								

Reported response rates and number of evaluable patients (in parentheses) by tumor type. Explanations: see Tables 1 and 5.

CONCLUSIONS

Doxorubicin scheduling has a major effect on the cardiotoxicity of the drug. Compared to the standard (high-dose rapid administration q 3 week) schedule, both q 1 week schedules and infusions lasting 24 h or longer lead to a measurable decrease of clinical and histological cardiac damage. A reduction of cardiac toxicity has so far not been shown for infusions of less than 24 h duration. While myelotoxicity does not seem to be altered to a great extent by schedule alterations, there is an increased risk of mucositis especially after prolonged infusions, but nausea and vomiting as well as alopecia are influenced favorably.

There is strong evidence that the threshold for damage to heart muscle cells is mainly related to the peak DOX concentrations, as these peak levels are much lower with the less cardiotoxic schedules. Obviously, a detoxifying mechanism must exist in heart muscle cells which become saturated at higher drug levels, but works more efficiently as long as saturation levels are not exceeded.

While the influence of scheduling on cardiotoxicity has been clearly demonstrated, much less can be said about clinical antitumor effectiveness. There is an astonishing lack of prospective, randomized trials comparing different methods of doxorubicin administration. So far, none of the different methods of DOX administration reviewed has shown a definite advantage as far as antitumor efficacy is concerned. This preliminary impression may change with future investigations. However, the available *in vitro* and *in vivo* data suggest that the antineoplastic effectiveness of DOX is mainly a function of tumor cell exposure to the drug, once an effective concentration threshold is exceeded. This leads to the assumption of different cardiotoxic and antineoplastic threshold concentrations for protracted application schedules.

More research concerning the concentration/time dependence of doxorubicin exposure remains to be done in order to define the effectiveness of the 'cardioprotective' modes of application. Randomized clinical trials comparing rapid and prolonged infusion schedules of doxorubicin should be performed.

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