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Review

Impact of Scheduling on Toxicity and Clinical Efficacy of Doxorubicin: What Do We Know in the Mid-Nineties?

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INTRODUCTION

ANTHRACYCLINES ARE among the most active agents against both solid tumours and haematological malignancies. Doxorubicin is the most widely used agent of this class [1]. Like other anthracyclines, it is associated with chronic cardiotoxicity [1, 2], producing biventricular, progressive congestive heart failure [3, 4]. The exact mechanisms by which doxorubicin and the other anthracyclines cause cardiac damage are still under debate [5]. Oxidative stress mediated by anthracycline–iron complexes has been implicated [1, 5, 7], as have the anthracyclines' C-13 alcohol metabolites, specifically their capability of impairing calcium homeostasis [8–11].

Soon after their introduction into the clinic, it became evident that the probability of developing congestive heart failure following anthracycline therapy was strongly related to the cumulative dose a patient had received [4, 13, 14]. Based upon experience from large retrospective series [4], it was assumed that cumulative doxorubicin doses not exceeding 450–550 mg/m^2 would be relatively safe to use. More recently, however, more and more evidence (usually from populations treated as children or adolescents) has been collected to show that this assumption needs to be revoked. Firstly, both invasive and non-invasive techniques have been successfully used to demonstrate subclinical cardiac damage in an extremely high percentage of patients treated with proposed 'safe' cumulative doses [15–20]. Depending on the sensitivity of the methods employed, the proportion of hearts found to be damaged has varied considerably. In some studies, most or even all hearts showed measurable damage [21–24]. Of even greater concern, substantial evidence has accumulated that cardiac function will continue to deteriorate even long after the discontinuation of anthracyclines, as witnessed by worsening subclinical indices of cardiac function [16–18, 24]. Steinherz and associates, when studying long-term survivors of childhood malignancy by echocardiography, saw 56 patients at least 10 years after a median anthracycline dose of 495 mg/m^2, and 38% of these had had abnormal systolic indices, compared with only 18% of 145 patients evaluated less than 10 years after therapy [17]. Afterload, proposed to be a more subtle indicator of chronic anthracycline cardiotoxicity, increased progressively in 24 of 34 patients evaluated serially by Lipshultz and colleagues [16]. In agreement with these findings which prove a continuing decline of subclinical cardiac parameters, many authors have reported cases of cardiac decompensation and death years or even decades after anthracycline treatment [18, 25–28]. With these dire consequences in mind, the need for a significant reduction of anthracycline cardiotoxicity becomes obvious.

APPROACHES TO REDUCE ANTHRACYCLINE CARDIOTOXICITY

Avoiding anthracyclines altogether in order to avoid their side-effects is generally not feasible, as adequate therapeutic alternatives are lacking. Premature termination of anthracycline therapy upon the development of subclinical damage, as recommended by the Cardiology Committee of the Childrens Cancer Study Group [29], will not prevent damage from occurring. The search for 'better' anthracyclines has so far not led to analogues which have been convincingly shown to be more than moderately less cardiotoxic at equieffective clinical dosages [30]. Based upon the presumption that anthracycline–iron complex mediated oxidative stress could well be the main reason for anthracycline cardiotoxicity, the iron chelator ICRF-187 has been used as a cardioprotector with some success [31, 32]. In addition, several modifications of anthracycline formulation, such as liposome encapsulation [33] or coupling to microspheres [34], have been developed in order to increase therapeutic range, but neither of these has, as yet, gained wide clinical acceptance.

A relatively simple approach towards the problem of anthracycline cardiotoxicity has been the development of less cardiotoxic application schedules. Two different 'cardioprotective' schedules have been developed: First, standard intermittent 3- or 4-weekly single-dose therapy can be replaced by the weekly application of split dosages [35–37]. Alternatively, the time allowed for anthracycline application can be prolonged from minutes to continuous infusions lasting hours [38–40], days [41, 42] or even weeks or months [43, 44]. Like any

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other 'cardioprotective' measure, a schedule suitable to replace conventional high-dose intermittent bolus or short-term infusional application should fulfill two requirements: First, reduction of cardiotoxicity should be demonstrated clinically, morphologically and with functional tests. Second, and maybe even more important, the anthracycline's antineoplastic effect must not be compromised. A beneficial effect on cardiotoxicity must by no means be offset by a reduced efficacy of the antineoplastic treatment.

EFFECTS OF SCHEDULE CHANGES ON CARDIOTOXICITY

What is currently known about the impact of scheduling on the cardiotoxicity of doxorubicin treatment? A significant reduction of cardiotoxicity can be achieved by modifying the application schedule. The reduction of clinical cardiotoxicity with weekly split-dose administration of doxorubicin has been most convincingly shown by von Hoff and associates, who reviewed thousands of patients' records and, overall, saw only 0.8% congestive heart failure compared to 2.9% after every 3 week administration [4]. Both a randomised study by Jain and colleagues [45] and a non-randomised, historically controlled study by Torti and coworkers [46] found less heart failure after weekly split-dose than after intermittent high-dose doxorubicin. Large groups of patients on weekly split-dose doxorubicin with a remarkably low incidence of congestive heart failure have also been reported by the Central Oncology Group [35, 36] and the Western Cancer Study Group [37, 47].

Not all studies have included monitoring of subclinical cardiotoxicity, but analyses of myocardial tissue obtained by endomyocardial biopsy have confirmed the reduced cardiotoxicity of weekly split-dose administration, finding less severe damage at equal cumulative doses [46, 48, 49]. Torti and associates have estimated that an additional 168 mg/m^2 could be given before causing the same amount of morphological damage as produced by an every 3 week high-dose schedule [46]. The reduced cardiotoxicity of weekly split-dose doxorubicin could also be confirmed by non-invasive testing of systolic cardiac function. Compared with every 3 week application, fewer cases of reduced left ventricular ejection fraction were observed by Jain and colleagues on multigated cardiac blood pool scans (0/26 versus 4/31) [45]. Valdivieso and coworkers, using m-mode echocardiography, measured median ejection fractions of 67.5% after a weekly regimen and of 61% after an every 3 week schedule [48].

An even more striking reduction of cardiotoxicity is observed when doxorubicin is not given as a bolus or by rapid infusion, but by continuous infusion, as investigators from the M.D. Anderson Cancer Center were able to demonstrate. At 500–800 mg/m^2 cumulative dose, they observed a 24% incidence of congestive heart failure after rapid administration, but none after 24- to 96-h continuous infusion. Doses over 800 mg/m^2 led to heart failure in 14% of patients given 24- to 48-h infusions and only 9% of patients given 96-h infusions [41]. These clinical findings were substantiated by endomyocardial biopsies showing markedly less morphological damage after continuous infusions, with 96-h application again causing fewer changes than 24 to 48 h infusions [41, 50, 51]. Several other groups have been able to confirm the low incidence of congestive heart failure after continuous infusions of doxorubicin. For example, significantly fewer cardiac events after 96-h infusions (1%) than after rapid application (8%) were observed in a randomised study of 240 soft tissue sarcoma patients performed by the Southwest Oncology Group (SWOG), even though cumulative doses were similar for both cohorts [52]. As for subclinical functional damage, no significant decrease of systolic function measured by radionuclide ventriculography was observed by Speyer and colleagues with 24-h continuous infusions [53] or Neglia and Woods with 96-h infusions [54], while Savage and Skubitz did notice further worsening of function in pretreated patients with abnormal baseline values [55]. Casper and colleagues, who randomised the application schedule of doxorubicin monotherapy for soft tissue sarcoma patients, saw radionuclide scan abnormalities in 61% of patients who had received a median cumulative dose of 420 mg/m^2 by bolus, compared to only 41% of patients who had received 540 mg/m^2 cumulative dose by continuous infusions over 96 h. The rate of cardiotoxicity as a function of cumulative doxorubicin was significantly higher in the former group [56].

When given as prolonged continuous infusions of only a few mg/m^2/d over weeks or months, doxorubicin seems to be even less cardiotoxic, with cumulative doses well above 1000 mg/m^2 having been applied this way [57–60]. Cardiotoxicity is not completely abolished even with this schedule, but clinical signs of congestive heart failure have rarely been observed and then only at very high cumulative doses in patients pretreated with bolus doxorubicin [58, 59].

How long must an infusion be in order to be 'cardioprotective'? The shortest duration for which such cardioprotection has been observed in a controlled, randomised study is 6 h. In a study performed by Shapiro and associates, none of 31 patients receiving 6 h infusions compared to 13% of 31 patients given bolus doxorubicin developed signs of cardiac dysfunction [40]. However, from the accumulated evidence, it seems that the longer the duration of the infusion of any fixed doxorubicin dose, the less severe its cardiotoxic effect will be. Unfortunately, no adequate long-term follow-up information is available to indicate whether this statement will hold true in the long term, or if trouble has only been postponed. Still, it is reasonable to expect that the acute cardioprotective effect observed will also translate into long-term benefit for the heart.

EFFECTS OF SCHEDULE CHANGES ON OTHER TOXICITIES

Non-cardiac side-effects are also influenced by doxorubicin scheduling. While myelotoxicity does not seem to be affected by giving doxorubicin as a continuous infusion [39, 49], neutropenia and infectious complications have been found less frequently with weekly split-doses as opposed to every 3 week schedules [48, 49]. Alopecia, nausea, vomiting and diarrhoea may also be reduced by weekly split-dose administration [49], but this has not been observed in all studies. Acute gastrointestinal upset is, however, certainly reduced with continuous infusions [42, 52], while mucositis becomes more prominent [39, 42, 50] and is dose-limiting for prolonged exposure [43, 44, 58]. The otherwise very unusual hand–foot syndrome is not so rarely observed with prolonged continuous infusions [59, 61]. As giving doxorubicin as a continuous infusion more or less requires the use of a central venous catheter, complications associated with this drug delivery system may occur [7, 57].

INFLUENCE OF SCHEDULING ON PHARMACOKINETICS

Why are split-dose or prolonged infusions of anthracyclines so much less cardiotoxic? The most obvious association is the marked reduction of peak plasma doxorubicin levels attained with these schedules [35, 41]. The available literature on pharmacokinetic–pharmacodynamic relationships of anthracyclines has recently been reviewed in detail [62]. Metabolic processing of doxorubicin administered by continuous infusion has been observed to be similar to that after rapid administration and to show no change with time [63]. While some influence of doxorubicin dose on plasma kinetics has been suggested [64] and both inter- and intrapatient variability may be substantial [63, 65], it appears that, for all practical purposes, pharmacokinetics may be assumed to be more or less linear within the clinical dose range [65–68]. Accordingly, peak plasma levels after weekly split-dose doxorubicin have been found to be reduced in proportion to those of control patients treated 3-weekly with higher dosages [69].

The reduction of peak plasma levels is much more pronounced (several orders of magnitude) when anthracyclines are given by continuous infusion. When correcting the peak levels for the applied dose, this correlation becomes even more apparent. The longer the time allowed for application, the lower the peak plasma level will be [70]. While levels of around 50 to over 100 ng/ml per mg/m^2 applied have been reported for bolus or short-term infusion schedules [66, 67, 71–75], they range from below 1 to around 2 ng/ml per mg/m^2 for infusions lasting 24 h or more [41, 72–77]. Legha and colleagues found doxorubicin levels after 96-h infusions to be significantly lower than after 48-h infusions, which were lower than after 24-h application, which in turn were much lower than after slow injections [41, 77]. When prolonged application of only a few milligrams per m^2 per day is chosen, levels are minimal at best, but often undetectable [44, 63, 78]. The reduced cardiotoxicity observed with liposomally encapsulated doxorubicin has also, among other things, been attributed to a prevention of peak plasma concentrations due to a protracted release from the liposomal depot [79].

In contrast to peak plasma levels, the area under the concentration time curve (AUC) in plasma has repeatedly been reported as being independent from infusion time, be it prolonged to hours or even days, both in animals [11] and in humans [66, 73–75, 80].

However, contradicting data claiming an enhancement of plasma AUC for doxorubicin and doxorubicinol with prolonged infusions have been published by Twelves and colleagues [72]. Their report also showed greater total exposure to doxorubicin with a weekly schedule of 25 mg/m^2 than with 75 mg/m^2 given every 3 weeks.

What about intracellular drug levels? In a study by Muller and colleagues, peak doxorubicin levels in chronic lymphocytic leukaemia cells, exposed *in vivo* to a 96-h infusion, were reduced, but only to 43% of those given rapid administration. Peak plasma levels, however, only amounted to 0.7%. In this study, intracellular AUC was compromised by continuous infusion [75]. In contrast, Speth and colleagues, investigating leukaemia blasts [73] and melanoma cells [74] found cellular doxorubicin AUC to be similar after rapid or continuous administration. For daunorubicin, the other classical anthracycline, one study even suggested an increased accumulation in human leukaemic cells with prolonged infusion [81]. Cardiac doxorubicin and doxorubicinol levels after 1-h and 24-h doxorubicin infusions have been evaluated in rabbits [11]. Here, as above, doxorubicin and doxorubicinol peak plasma levels, but not AUC, were lower after the protracted infusion. Peak left ventricular doxorubicin was almost five times higher with the 1-h infusion, peak doxorubicinol about 2.5 times higher. When the animals were sacrificed 7 days after dosing, the tissue levels of both compounds were no longer correlated to the application schedule. The authors postulated that cardioprotection following infusion might be related to attenuation of the peak plasma or cardiac concentration of doxorubicin or doxorubicinol, but warned, as had others previously, that anthracyclines [82] or their 7-OH metabolites [8] might accumulate in the heart with repeated dosing [11]. Continuous infusion does not seem to prevent this prolonged anthracycline accumulation in the myocardium [10, 79]. After five doses given to rats either by bolus or as 24-h infusions, for example, similar cardiac doxorubicin concentrations were present in both groups [79].

SCHEDULE AND *IN VITRO* ACTIVITY

In vitro studies might help to clarify if high anthracycline concentrations, as achieved clinically with bolus or rapid infusion techniques, or prolonged exposure time, as with continuous infusion, would be more effective against neoplastic cells. However, no clear conclusions can be drawn from the available *in vitro* studies which have produced conflicting results (for review see [83]).

From experiments in Chinese hamster and HeLa cells, Eichholtz-Wirth came to the conclusion that the cytotoxic effect of doxorubicin was proportional to both the extracellular drug concentration and the time of exposure [84], consistent with later reports that found no schedule dependency of doxorubicin activity against various cell lines at equal concentration × time values *in vitro* [85–87]. Other experiments, however, suggested a superiority of high-dose, short exposure over low-dose, long exposure incubation in, among others, bone marrow cells [88], cultured murine sarcoma [89] or rat glioblastoma cells [90]. In contrast, others found greater cell kill with low-dose, long incubations for normal and leukaemic human haematopoietic cells [76, 91, 92] or sarcoma 180 cells [93]. Milano and associates, working with four breast cancer lines, found that doxorubicin pulses on top of continuous exposure (thereby mimicking split-dose dose application) resulted in greater cytotoxicity than continuous exposure alone. They attributed their findings to the greater intracellular doxorubicin concentration reached by pulsatile exposure [94].

The expression of the multidrug resistance gene *MDR1* can be rapidly upregulated by anthracyclines [95]. In one *in vitro* study, a single 24-h contact to doxorubicin induced the P-glycoprotein (Pgp) far more effectively than 1-h exposure [96]. On the other hand, experiments in several colon carcinoma, Pgp-anthracycline resistant cell lines showed that the drug exposure needed to achieve a given cell kill was reduced as much as 9-fold when cells were treated for 7 days as compared with 3-h exposure. In contrast, drug exposure had to be increased under conditions of continuous treatment in cell lines where P-glycoprotein played a lesser role [97].

ARE LESS CARDIOTOXIC DOXORUBICIN SCHEDULES STILL EFFECTIVE?

Past as well as more recent reviews and editorials, dealing with the pertinent literature, have again and again lamented

the paucity of controlled trials assessing the influence of anthracycline schedule on antineoplastic efficacy [61, 62, 70, 83, 98], which stands in stark contrast to the flood of studies in which altered schedules are used in a completely uncontrolled manner. In fact, when reviewing the literature in 1989, we were unable to find a single completed randomised study addressing the efficacy of continuous infusion doxorubicin [70]. Most of the few controlled studies published since then suffer from serious limitations and major confounding factors. Trials have often been performed in tumours with very poor prognosis and, at best, limited responsiveness to anthracyclines. Therefore, response and survival could be expected to be poor regardless of the schedule used. The use of anthracyclines as part of combination chemotherapy, often associated with additional treatment variables, makes interpretation even more difficult. A synopsis of controlled trials on doxorubicin scheduling is given below and in Table 1, together with some relevant results obtained with the related anthracyclines daunorubicin and epirubicin.

DOXORUBICIN SCHEDULING IN THE TREATMENT OF SARCOMA

Two randomised trials on the treatment of adult soft tissue sarcoma with either bolus or continuous infusion doxorubicin have been published [52, 56]. A randomised co-operative SWOG trial used doxorubicin plus dacarbazine both given either as a bolus or a 96-h continuous infusion for metastatic disease. Similar overall response rates (17%), complete response rates (5%), median response duration and survival were observed in both study arms. As mentioned, the schedule of dacarbazine was altered in parallel to that of doxorubicin, thereby possibly obscuring any effect that anthracycline scheduling might have had [52]. Investigators from the Memorial Sloan Kettering Cancer Center gave doxorubicin, either by bolus or by 72-h continuous infusion, as adjuvant monotherapy for high-grade soft tissue sarcomas. A preliminary report of that study indicated inferior survival in the continuous infusion group [107]. Multivariate analysis, however, selected three other criteria, but not doxorubicin schedule, as an unfavourable characteristic [56]. An earlier study comparing weekly split-dose with every 3 week doxorubicin for metastatic soft tissue sarcoma reported similar (but again very poor) response in both arms [99].

Before jumping to generalised conclusions about the efficacy of different doxorubicin schedules from these studies, it must be remembered that soft tissue sarcoma in adults, which includes a mixture of different tumour types with varying clinical behaviour, is, as a whole, hardly the prime example of a chemosensitive tumour. The benefit, if any, of chemotherapy for this tumour entity, at least in the adjuvant setting, remains poorly defined [108].

A negative impact of continuous infusion doxorubicin on response rates of osteosarcoma to pre-operative chemotherapy, as initially observed in a preliminary report of sequential studies by our COSS (Cooperative Osteosarcoma Study Group) group [109], has not been validated by further analysis. Histological response of 140 patients treated with one single rapid infusion of 90 mg/m^2 as part of a 10 week, four drug pre-operative regimen for osteosarcoma at 71% did not differ significantly from the 65% observed in 81 patients receiving a 48-h infusion within the same protocol. With postoperative continuation of polychemotherapy up to a cumulative doxorubicin dose of 360–450 mg/m^2, projected metastasis-free survival rates were also not significantly influenced by anthracycline scheduling [100]. As a recent meta-analysis found, doxorubicin dose intensity is an important determinant of favourable outcome for osteogenic sarcoma [110], and it should be expected that any major loss of efficacy by doxorubicin schedule alterations, if present, would have been detected by the COSS group. The results obtained by Benjamin and colleagues in 97 patients with primary osteosarcoma by using 96-h infusions of doxorubicin in combination with cisplatinum [111] are in the same range as those of trials using rapid application, again arguing against a major impairment of doxorubicin activity by continuous infusion scheduling in this tumour type.

DOXORUBICIN SCHEDULING IN THE TREATMENT OF BREAST CANCER

Sequential trials of three doxorubicin schedules within the FAC (5-fluorouracil, doxorubicin, cyclophosphamide) regimen in 274 women with previously untreated, measurable breast cancer performed at the M.D. Anderson Cancer Center failed to detect any influence of doxorubicin schedule on response rates, with approximately 20% complete and 80% overall responses regardless of schedule. The duration of response tended to be slightly longer in the continuous infusion group, attributed to the possibility of longer treatment for responding tumours with the less cardiotoxic schedule [42].

A plethora of uncontrolled studies using weekly split-dose doxorubicin or weekly split-dose epirubicin for breast cancer has been published. In a recent paper, Blomqvist and associates were able to cite 22 such reports, with response rates ranging from 12% to 47% [112]. Unfortunately, much less effort has gone into studies randomising the schedule. One such randomised trial, initiated to compare three different dosing schedules of single agent doxorubicin, was terminated before any conclusions about the comparative efficacy could be reached [101]. A British study of single agent doxorubicin found equivalent activity for every 3 week and weekly split-dose doxorubicin at equal dose intensity [102, 113]. The same holds true for studies by Jain and colleagues [64] and Gundersen and colleagues [103], which, however, included other variables. A single randomised study comparing weekly split-dose with every 4 week epirubicin for metastatic breast cancer within the FEC (5-fluorouracil, epirubicin, cyclophosphamide) protocol reported better results for the monthly schedule [112]. It remains to be seen if these results, which the authors themselves described as unexpected, can be reproduced.

DOXORUBICIN SCHEDULING IN THE TREATMENT OF LUNG CANCER

For small-cell lung cancer, a randomised trial by Anderson and associates, giving doxorubicin either by bolus or by continuous 7 day infusion as part of a combination regimen including ifosfamide and oral etoposide, found no impact of scheduling on response. Any conclusion as to the comparative efficacy of the two anthracycline schedules must be guarded, because the schedule of ifosfamide was altered in parallel to that of doxorubicin. The extremely poor outlook for patients treated with the more conventional bolus approach (median survival of 25 weeks, 2 year survival 5%) would make it almost impossible to detect any loss of activity by infusional scheduling [104, 114]. The two published randomised studies

Table 1. Doxorubicin scheduling and treatment outcome

Author	[Ref.]	Tumour type	Dose (mg/m²)	Schedule	*n*	RR	RD	OS	Other drugs
Borden	[99]	STS*	70	RI-3 wk	94	18%	3 mo†	8 mo	None
randomised			15‡	RI-1 wk	88	17%	2 mo†	8 mo	None
Zalupski	[52]	STS*	60	RI	118	17%	20 mo§	11 mo	DAC-Bolus
randomised			60	CI-96 h	122	17%	13 mo§	11 mo	DAC-CI‖
Casper	[56]	STS¶	60	RI	41	Schedule not a risk factor			None
randomised			60	CI-72 h	41				None
Bielack	[100]	OSTEO	90	RI	140	71%		75%**	MTX,DDP,IFO
sequential			90	CI-48 h	81	65%		66%**	MTX,DDP,IFO
Hortobagyi	[42]	BREAST	50	RI	133	81%	13 mo	27 mo	CYC,5-FU
sequential			50	CI-48 h	79	80%	14 mo	24 mo	CYC,5-FU
				CI-96 h	62	76%			CYC,5-FU
Lokich	[101]	BREAST*	60	RI-3 wk	67††	25%			None
randomised			20	RI-1 wk		33%			None
			15	CI-96 h		44%			None
Richards	[102]	BREAST*	75	RI-3 wk	28	50%†	4 mo	8 mo	None
randomised			25	RI-1 wk	31	58%†	5 mo	8 mo	None
Jain	[45]	BREAST*	37.5	RI-4 wk	31	45%	8 mo		MITOX
randomised			12.5	RI-1 wk	26	42%	9 + mo		MITOX
Gundersen	[103]	BREAST*	50	RI-3 wk	66	36%	8 + wk	Equal	CYC,VCR
randomised			20	RI-1 wk	62	31%	12 + wk		None‖
Valdivieso	[48]	NSCLC	60	RI-3 wk	42	19%	21 wk	32 wk	CYC,DDP,FT
randomised			20	RI-1 wk	45	31%	33 wk	37 wk	CYC,DDP,FT
Umsawadi‡‡	[49]	NSCLC	60	CI-6 h/3 wk	51	31%	11 wk	–	CYC,DDP
randomised			20	RI-1 wk	51	35%	36 wk	–	CYC,DDP
Anderson	[104]	SCLC	35	RI	78	64%	20 wk	25 wk	IFO-Bolus,VP
randomised			35	CI-168 h	70	69%	26 wk	30 wk	IFO-CI,VP‖
Souhami	[105]	SCLC	50	RI-3 wk	217	81%		11 mo	CYC,VCR,DDP,VP
randomised			25	RI-1 wk	221	82%		11 mo	IFO,DDP,VP‖
Sculier	[106]	SCLC	50	RI-3 wk	101	62%	35 wk	43 wk	6 drugs
randomised			25	RI-1 wk	98	69%	39 wk	49 wk	3 drugs

Randomised and sequential trials comparing the efficacy of different doxorubicin schedules. For comments on specific trial designs and results, see text.

n, number of patients; RR, response rate; RD, response duration; OS, overall survival; wk, weeks; mo, months; STS, soft tissue sarcoma; OSTEO, osteosarcoma; BREAST, breast cancer; (N)SCLC, (non-)small-cell lung cancer; RI, rapid infusion; 3 wk or 4 wk, intermittent high-dose; 1 wk, weekly split-dose; CI, continuous infusion; DAC, actinomycin-D; MTX, methotrexate; DDP, cisplatinum; IFO, ifosfamide; CYC, cyclophosphamide; 5-FU, 5-fluorouracil; MITOX, mitoxantrone; VCR, vincristine; FT, ftorafur; VP, etoposide.

*Advanced or metastatic; †Time to progression; ‡Plus initial loading dose; §For CR, 6.6/9.3 months for PR; ‖Schedule of accompanying drugs varies between the two anthracycline schedules; ¶Adjuvant; **Three year metastasis-free survival; ††Total number of patients combined; ‡‡RR for patients with limited disease (LD), no prior radiotherapy (RT). RR for LD, prior RT 25/20%, for extended disease 11/16%.

on weekly split-dose versus every 3 week doxorubicin in small-cell lung cancer have led to comparable results for both schedules, but the accompanying chemotherapy differed markedly between both study arms in both cases [105, 106].

In non-small-cell lung cancer, two randomised combination chemotherapy studies from the M.D. Anderson Cancer Center found no significant impact of giving weekly split-dose or 3-weekly doxorubicin at equal dose intensity on response rate or survival [48, 49], but response duration tended to be longer with the weekly regimen [49].

ANTHRACYCLINE SCHEDULING IN HAEMATOLOGICAL MALIGNANCIES

Preisler and colleagues have correlated individual plasma doxorubicin levels with the outcome of remission induction in acute non-lymphoblastic leukaemia (ANLL) [115]. This proposed correlation of measured anthracycline levels with antileukaemic effect could, however, not be reproduced by others such as Speth and colleagues [73]. Remission rates comparable or even superior to conventional administration have been claimed for fractionated anthracycline therapy [116], which can be expected to produce lower anthracycline levels. Effectiveness has also been observed with continuous anthracycline infusions as part of various combination regimens in uncontrolled settings [117–119]. We are not aware of any controlled studies on anthracycline scheduling in ANLL.

A randomised, upfront therapeutic window approach comparing a 24-h with a 1-h infusion of daunorubicin has been adopted by the German COALL (Cooperative Acute Lymphoblastic Leukaemia Study Group) group in children with *de*

novo acute lymphoblastic leukaemia. The proportional decline of blasts in peripheral blood was not affected by daunorubicin scheduling [120]. Another randomised comparison by Steinherz and colleagues in a very small group of 15 paediatric ALL patients even suggested a more rapid cytoreduction after 48-h continuous infusion of daunorubicin than after rapid application of the drug [121]. In again another paper, similar low rates of induction failure were seen with two multi-agent protocols incorporating either weekly split-dose daunorubicin or a single 2-day course [122].

Ninety-six-hour infusional doxorubicin in combination with other agents has led to remissions in some patients with relapsed or poor risk non-Hodgkin's lymphoma, even in some refractory to bolus treatment [123, 124]. The role of the doxorubicin infusion in this setting is obscured by the inclusion of etoposide in the reported protocols, a drug with well known schedule dependency, favouring protracted application [125].

No schedule-dependent differences of tumour regression or survival were found in a randomised trial of bolus versus 24-h doxorubicin in rats with experimental IgM immunocytoma [79]. In humans, infusional 96-h doxorubicin together with infusional vincristine and oral dexamethasone (VAD) has been given with some success as first-line [126] or second-line (including patients refractory to bolus doxorubicin) [127] therapy for multiple myeloma. Compared to literature data obtained with this infusional regime, an intermittent bolus approach with the same three drugs yielded inferior response and survival [128]. Another report of slow versus fast infusion of the three agents in 31 patients treated sequentially at one institution found good responses in 31% versus 20% and survival times of 17 versus 9 months, but interpreted these results as similar [129].

We have not been able to find adequately controlled trials for any of the other malignancies against which continuous infusion doxorubicin is being used.

CONCLUSION

Substantial evidence supports the claim that doxorubicin schedules leading to lower peak drug levels in plasma than those produced by intermittent high-dose rapid application, are much less cardiotoxic. Are such changes of doxorubicin scheduling oncologically safe? The available *in vitro* and *in vivo* data argue against a proportional decline of clinical efficacy together with that of cardiotoxicity. Does this mean that the less cardiotoxic schedules can be used without any risk? Not necessarily: complete equi-effectivity of these schedules has still, after more than a quarter of a century of doxorubicin therapy, not been proven unequivocally. More and better designed controlled studies are needed before it can be assumed that the 'cardiotoxic' and the 'cardioprotective' schedules are of absolutely identical antitumoural activity. In view of the currently available clinical evidence, schedule alterations seem to offer a realistic chance to minimise the harmful cardiac effects of anthracyclines without necessarily reducing their efficacy.

1. Myers CE, Chabner BA. Anthracyclines. In Chabner BA, Collins JM, eds. *Cancer Chemotherapy. Principles and Practice*. Philadelphia, J.B. Lippincott Company, 1990, 356–381.
2. Billingham ME, Mason JW, Bristow MR, Daniels JR. Anthracycline cardiomyopathy monitored by morphological changes. *Cancer Treat Rep* 1978, **62**, 865–872.
3. Lefrak EA, Pitha J, Rosenheim S, *et al.* A clinicopathological analysis of adriamycin cardiotoxicity. *Cancer* 1973, **32**, 302–314.
4. von Hoff DD, Layard MW, Basa P, *et al.* Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979, **91**, 710–717.
5. Olson RD, Mushlin PS. Doxorubicin cardiotoxicity: analysis of prevailing hypotheses. *FASEB J* 1990, **4**, 3076–3086.
6. Olson RD, Boerth RC, Gerber JG, Nies AS. Mechanism of adriamycin cardiotoxicity: evidence for oxidative stress. *Life Sci* 1981, **29**, 1393–1401.
7. Basser RL, Green MD. Strategies for prevention of anthracycline cardiotoxicity. *Cancer Treat Rev* 1993, **19**, 57–77.
8. del Tacca M, Danesi R, Ducci M, Bernardini C, Romanini A. Might adriamycinol contribute to adriamycin-induced cardiotoxicity? *Pharmacol Res Commun* 1985, **17**, 1073–1084.
9. Boucek RJ, Olson RD, Brenner DE, Ogunbumni EM, Inui M, Fleischer S. The major metabolite of doxorubicin is a potent inhibitor of membrane-associated ion pumps. *J Biol Chem* 1987, **262**, 15851–15856.
10. Cusack BJ, Mushlin PS, Voulelis LP, Li X, Boucek RJ Jr, Olson RD. Daunorubicin-induced cardiac injury in the rabbit: a role for daunorubicinol? *Toxicol Appl Pharmacol* 1993, **118**, 177–185.
11. Cusack BJ, Young SP, Driskell J, Olson RD. Doxorubicin and doxorubicinol pharmacokinetics and tissue concentrations following bolus injection and continuous infusion of doxorubicin in the rabbit. *Cancer Chemother Pharmacol* 1993, **32**, 53–58.
12. Benjamin RS, Wiernik PH, Bachur NR. Adriamycin chemotherapy: efficacy, safety, and pharmacological basis of an intermittent single high-dosage schedule. *Cancer* 1973, **33**, 19–27.
13. Gottlieb JA, Lefrak EA, O'Bryan RM, *et al.* Fatal adriamycin cardiomyopathy: prevention by dose limitation. *Proc Annu Meet Am Assoc Cancer Res* 1973, **14**, 88.
14. von Hoff DD, Layard M. Risk factors for development of daunorubicin cardiotoxicity. *Cancer Treat Rep* 1981, **65** (Suppl. 4), 19–23.
15. Hausdorf G, Morf G, Beron G, *et al.* Long term doxorubicin cardiotoxicity in childhood: non-invasive evaluation of the contractile state and diastolic filling. *Br Heart J* 1988, **60**, 309–315.
16. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med* 1991, **324**, 808–815.
17. Steinherz LJ, Steinherz PG, Tan CTC, Heller G, Murphy ML. Cardiotoxicity 4–20 years after completing anthracycline therapy. *JAMA* 1991, **266**, 1672–1677.
18. Geidel S, Garn M, Grävinghoff L, *et al.* Cardiomyopathy after treatment for osteosarcoma: a contribution to cardiotoxicity of adriamycin. *Klin Pädiatr* 1991, **203**, 257–261.
19. Bu'Lock FA, Mott MG, Oakhill A, Martin RP. Left ventricular diastolic function after anthracycline chemotherapy in childhood: relation with systolic function, symptoms, and pathophysiology. *Br Heart J* 1995, **73**, 340–350.
20. Lang D, Hilger F, Binswanger J, Andelfinger G, Hartmann W. Late effects of anthracycline therapy in childhood in relation to the function of the heart at rest and under physical stress. *Eur J Pediatr* 1995, **154**, 340–345.
21. Druck MN, Gulenchyn KY, Evans WK, *et al.* Radionuclide angiography and endomyocardial biopsy in the assessment of doxorubicin cardiotoxicity. *Cancer* 1984, **53**, 1667–1674.
22. Maione S, Giunta A, Tuccillo B, *et al.* Doppler echocardiographic assessment of left ventricular function in patients with primary lung cancer treated with doxorubicin. *Tumori* 1988, **74**, 725–729.
23. Marchandise B, Schroeder E, Bosly A, *et al.* Early detection of doxorubicin cardiotoxicity: interest of Doppler echocardiographic analysis of left ventricular filling dynamics. *Am Heart J* 1989, **118**, 92–98.
24. Lipshultz SE, Lipsitz SR, Mone SM, *et al.* Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med* 1995, **332**, 1738–1743.
25. Gottlieb SL, Edminston WA, Haywood LJ. Late, late doxorubicin cardiotoxicity. *Chest* 1980, **78**, 880–882.
26. Steinherz LJ, Steinherz P. Cardiac failure more than six years post anthracyclines. *Am J Cardiol* 1988, **62**, 505 (Abstract).
27. Goorin AM, Chauvenet AR, Perez-Atayde AR, Cruz J, McKone R, Lipshultz SE. Initial congestive heart failure, six to ten years

after doxorubicin chemotherapy for childhood cancer. *J Pediatr* 1990, **116**, 144–147.
28. Steinherz LJ, Steinherz PG, Tan C. Cardiac failure and dysrhythmias 6–19 years after anthracycline therapy: a series of 15 patients. *Med Pediat Oncol* 1995, **24**, 352–361.
29. Steinherz LJ, Graham T, Hurwitz R, *et al.* Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the Cardiology Committee of the Children's Cancer Study Group. *Pediatrics* 1992, **89**, 942–949.
30. Weiss RB. The anthracyclines: will we ever find a better doxorubicin? *Semin Oncol* 1992, **19**, 670–686.
31. Wexler LH, Berg S, Andrich M, *et al.* ICRF-187 reduces doxorubicin-induced cardiotoxicity with no impact on response to chemotherapy. *Proc Annu Meet Amer Soc Clin Oncol* 1993, **29**, A1434.
32. Speyer JL, Green MD, Zeleniuch-Jacquotte A, *et al.* ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. *J Clin Oncol* 1992, **10**, 117–127.
33. Herman EH, Rahman A, Ferrans VJ, Vick JA, Schein PS. Prevention of chronic doxorubicin cardiotoxicity in beagles by liposomal encapsulation. *Cancer Res* 1983, **43**, 5427–5432.
34. Napoli S, Burton MA, Martins IJ, Chen Y, Codde JP, Gray BN. Dose response and toxicity of doxorubicin microspheres in a rat tumor. *Anticancer Drugs* 1992, **3**, 47–53.
35. Weiss AJ, Metter GE, Fletcher WS, *et al.* Studies on adriamycin using a weekly regimen demonstrating its clinical effectiveness and lack of cardiac toxicity. *Cancer Treat Rep* 1976, **60**, 813–822.
36. Weiss AJ, Manthel RW. Experience with the use of adriamycin in combination with other anticancer agents using a weekly schedule, with particular reference to lack of cardiac toxicity. *Cancer* 1977, **40**, 2046–2052.
37. Chlebowski RT, Paroly WS, Pugh RP, *et al.* Adriamycin given as a weekly schedule without a loading course: clinically effective with reduced incidence of cardiotoxicity. *Cancer Treat Rep* 1980, **64**, 47–51.
38. Gercovich FG, Praga C, Beretta G, *et al.* Ten-hour continuous infusion of adriamycin. *Proc Annu Meet Am Assoc Cancer Res and ASCO* 1979, **20**, 372 (Abstract).
39. Green MD, Speyer JS, Bottino JC, Blum RH, Wernz JC, Muggia FM. Phase I–II study of the continuous infusion of doxorubicin in the treatment of non-small cell lung cancer. *Cancer Treat Rep* 1984, **68**, 681–682.
40. Shapiro J, Gotfried M, Lishner M, Ravid M. Reduced cardiotoxicity of doxorubicin by a 6-hour infusion regimen. A prospective randomized evaluation. *Cancer* 1990, **65**, 870–873.
41. Legha SS, Benjamin RS, Mackay B, *et al.* Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med* 1982, **96**, 133–139.
42. Hortobagyi GN, Frye D, Buzdar AU, *et al.* Decreased cardiac toxicity of doxorubicin administered by continuous infusion in combination chemotherapy for metastatic breast carcinoma. *Cancer* 1989, **63**, 37–45.
43. Lokich J, Bothe T, Zipoli R, *et al.* Constant infusion schedule for adriamycin. A phase I–II clinical trial of a 30-day schedule by ambulatory pump delivery system. *J Clin Oncol* 1983, **1**, 24–28.
44. Garnick MB, Weiss GR, Steele GD, *et al.* Clinical evaluation of long term, continuous-infusion doxorubicin. *Cancer Treat Rep* 1983, **67**, 133–142.
45. Jain K, Wittes R, Benedetto P, *et al.* A randomized comparison of weekly (Arm I) Vs. monthly (Arm II) doxorubicin (DOX) in combination with mitomycin C (MMC) in advanced breast cancer. *Proc Annu Meet Am Soc Clin Oncol* 1983, **2**, 109 (Abstract).
46. Torti FM, Bristow MR, Howes AE, *et al.* Reduced cardiotoxicity of doxorubicin delivered on a weekly schedule. *Ann Intern Med* 1983, **99**, 745–749.
47. Chlebowski RT, Bull F, Irwin L, Pugh R, Weiner JM, Bateman JR. Doxorubicin and methotrexate on a weekly schedule in patients with sarcomas. *Oncology* 1987, **44**, 210–213.
48. Valdivieso M, Burgess MA, Ewer MS, *et al.* Increased therapeutic index of weekly doxorubicin in the therapy of non-small cell lung cancer: a prospective, randomized study. *J Clin Oncol* 1984, **2**, 207–214.
49. Umsawadi T, Valdivieso M, Booser DJ, *et al.* Weekly doxorubicin versus doxorubicin every 3 weeks in cyclophosphamide, doxorubicin, and cisplatin chemotherapy for non-small cell lung cancer. *Cancer* 1989, **64**, 1995–2000.
50. Legha SS, Benjamin RS, Mackay B, *et al.* Adriamycin therapy by continuous intravenous infusion in patients with metastatic breast cancer. *Cancer* 1982, **49**, 1762–1766.
51. Legha SS, Benjamin RS, Ewer M, *et al.* Continuous intravenous infusion of adriamycin: evaluation of its efficacy and toxicity. *Excerpta Med Int Congr Ser* 1984, **629**, 378–386.
52. Zalupski M, Metch B, Balcerzak S, *et al.* Phase III comparison of doxorubicin and dacarbazine given by bolus versus infusion in patients with soft tissue sarcomas: a Southwest Oncology Group study. *J Natl Cancer Inst* 1991, **83**, 926–932.
53. Speyer JL, Bottino J, Nidus B, *et al.* Adriamycin (ADM) 24 hour infusion: a phase I trial. *Proc Annu Meet Am Assoc Cancer Res and ASCO* 1981, **22**, 363 (Abstract).
54. Neglia JP, Woods WG. Continuous-infusion doxorubicin in the treatment of primary hepatic malignancies of childhood. *Cancer Treat Rep* 1986, **70**, 655–657.
55. Savage PD, Skubitz KM. Continuous infusion chemotherapy for soft tissue sarcomas. *Proc Annu Meet Am Soc Clin Oncol* 1989, **8**, A1249.
56. Casper ES, Gaynor JJ, Hajdu SI, *et al.* A prospective randomized trial of adjuvant chemotherapy with bolus versus continuous infusion of doxorubicin in patients with high-grade extremity soft tissue sarcoma and an analysis of prognostic factors. *Cancer* 1991, **68**, 1221–1229.
57. Jasmin C, Gil-Delgado MA, Marino JP, Ecstein E, Descorps-Declere A, Misset JL. Phase I–II constant infusion of adriamycin (doxorubicin) by ambulatory pump delivery system in heavily pretreated (including adriamycin) breast cancer patients. *Ann Oncol* 1990, **1**, 189–193.
58. Vogelzang NJ, Ruane M, DeMeester TR. Phase I trial of an implanted battery-powered, programmable drug delivery system for continuous doxorubicin administration. *J Clin Oncol* 1985, **3**, 407–414.
59. Samuels BL, Vogelzang NJ, Ruane M, Simon MA. Continuous venous infusion of doxorubicin in advanced sarcomas. *Cancer Treat Rep* 1987, **71**, 971–972.
60. Bode U, Schmalenbach U. Doxorubicin Dauerinfusionen. Eine Pilotstudie bei jugendlichen Patienten. *Klin Pädiatr* 1988, **200**, 271–273.
61. DelaFlor-Weiss E, Uziely B, Muggia FM. Protracted drug infusions in cancer treatment: an appraisal of 5-fluorouracil, doxorubicin, and platinums. *Ann Oncol* 1993, **4**, 723–733.
62. de Valeriola D. Dose optimization of anthracyclines. *Anticancer Res* 1994, **14**, 2307–2314.
63. Sweatman TW, Lokich JL, Israel M. Clinical pharmacology of continuous infusion doxorubicin. *Ther Drug Monit* 1989, **11**, 3–9.
64. Boston RC, Phillips DR. Evidence of possible dose-dependent doxorubicin plasma kinetics in man. *Cancer Treat Rep* 1983, **67**, 63–69.
65. Robert J, Bui NB, Vrignaud P. Pharmacokinetics of doxorubicin in sarcoma patients. *Eur J Clin Pharmacol* 1987, **31**, 695–699.
66. Eksborg S, Strandler HS, Edsmyr F, Näslund I, Tahvanainen P. Pharmacokinetic study of IV infusions of adriamycin. *Eur J Clin Pharmacol* 1985, **28**, 205–212.
67. Erttmann R, Erb N, Steinhoff A, Landbeck G. Pharmacokinetics of doxorubicin in man: dose and schedule dependence. *J Cancer Res Clin Oncol* 1988, **114**, 509–513.
68. Bronchud MH, Margison RF, Howell A, Lind M, Lucas SB, Wilkinson PM. Comparative pharmacokinetics of escalating doses of doxorubicin in patients with metastatic breast cancer. *Cancer Chemother Pharmacol* 1990, **25**, 435–439.
69. Frenay M, Milano G, Renee N, *et al.* Pharmacokinetics of weekly low dose doxorubicin. *Eur J Cancer Clin Oncol* 1989, **25**, 191–195.
70. Bielack SS, Erttmann R, Winkler K, Landbeck G. Doxorubicin: effect of different schedules on toxicity and anti-tumor efficacy. *Eur J Cancer Clin Oncol* 1989, **25**, 873–882.
71. Rossi C, Gasparini G, Canobbio L, *et al.* Doxorubicin distribution in human breast cancer. *Cancer Treat Rep* 1987, **71**, 1221–1226.
72. Twelves CJ, Dobbs NA, Aldhous M, Harper PG, Rubens RD, Richards MA. Comparative pharmacokinetics of doxorubicin given by three different schedules with equal dose intensity in

patients with breast cancer. *Cancer Chemother Pharmacol* 1991, **28**, 302–307.
73. Speth PA, Linssen PCM, Boezemann JBM, Wessels HMC, Haanen C. Cellular and plasma adriamycin concentrations in long-term infusion therapy of leukemia patients. *Cancer Chemother Pharmacol* 1987, **20**, 305–310.
74. Speth PA, Linssen PCM, Holdrinet RGS, Haanen C. Plasma and cellular adriamycin concentrations in patients with myeloma treated with ninety-six-hour continuous infusion. *Clin Pharmacol Ther* 1987, **41**, 661–665.
75. Muller C, Chatelut E, Gualano V, *et al.* Cellular pharmacokinetics of doxorubicin in patients with chronic lymphocytic leukemia: comparison of bolus administration and continuous infusion. *Cancer Chemother Pharmacol* 1993, **32**, 379–384.
76. Raijmakers R, Speth P, de Witte T, Linssen P, Wessels J, Haanen C. Infusion-rate independent cellular adriamycin concentrations and cytotoxicity to human bone marrow clonogenic cells (CFU-GM). *Br J Cancer* 1987, **56**, 123–126.
77. Legha SS, Benjamin RS, Yap HY. Augmentation of adriamycin's therapeutic index by prolonged continuous I.V. infusion for advanced breast cancer. *Proc Annu Meet Am Assoc Cancer Res* 1979, **20**, 261 (Abstract).
78. Ackland SP, Ratain MJ, Vogelzang NJ, Choi KE, Ruane M, Sinkule SA. Pharmacokinetics and pharmacodynamics of long-term continuous-infusion doxorubicin. *Clin Pharmacol Ther* 1989, **45**, 340–347.
79. Storm G, van Hoesel QGCM, de Groot G, Kop W, Steerenberg PA, Hillen FC. A comparative study on the antitumor effect, cardiotoxicity and nephrotoxicity of doxorubicin given as a bolus, continuous infusion or entrapped in liposomes in the lou/M Wsl rat. *Cancer Chemother Pharmacol* 1989, **24**, 341–348.
80. Brenner DE, Grosh WW, Noone R, Stein R, Greco FA, Hande KR. Human plasma pharmacokinetics of doxorubicin: comparison of bolus and infusional administration. *Cancer Treat Symp* 1984, **3**, 77–83.
81. Paul C, Tidefeld U, Liliemark J, Peterson C. Increasing the accumulation of daunorubicin in human leukaemia cells by prolonging the infusion time. *Leukemia Res* 1989, **13**, 191–196.
82. Timour Q, Nony P, Lang J, Lakhal M, Trllet V, Faucon G. Doxorubicin concentration time course in the myocardium after single administration to the dog. *Cancer Chemother Pharmacol* 1987, **20**, 267–269.
83. Robert J. Continuous infusion or intravenous bolus: what is the rationale for doxorubicin administration? *Cancer Drug Deliv* 1987, **4**, 191–199.
84. Eichholtz-Wirth H. Dependence of the cytostatic effect of adriamycin on drug concentration and exposure time in vitro. *Br J Cancer* 1980, **41**, 886–891.
85. Carmichael J, de Graff WG, Gazdar A, Minna JD, Mitchell JB. Evaluation of a tetrazolium-based semi-automated colorimetric assay: assessment of chemosensitivity testing. *Cancer Res* 1987, **47**, 936–942.
86. Mergenthaler HG, Bruhl P, Ehninger G, Heidemann E. Comparative in vitro toxicity of mitoxantrone and adriamycin in human granulocyte-macrophage progenitor cells. *Cancer Chemother Pharmacol* 1987, **20**, 8–12.
87. Yang KP, Famaan NA. Lethal efficacy of doxorubicin on human medullary thyroid carcinoma cells in vitro. *Anticancer Res* 1988, **8**, 245–248.
88. Andersson B, Beran M, Peterson C, Tribukait B. Significance of cellular pharmacokinetics for the cytotoxic effects of daunorubicin. *Cancer Res* 1982, **42**, 178–183.
89. Nguyen-Ngoc T, Vrignaud P, Robert J. Cellular pharmacokinetics of doxorubicin in cultured mouse sarcoma cells originating from autochtonous tumors. *Oncology* 1984, **41**, 55–60.
90. Vrignaud P, Londos-Gagliardi D, Robert J. Cellular pharmacology of doxorubicin in sensitive and resistant rat glioblastoma cells in culture. *Oncology* 1986, **43**, 60–66.
91. Bailey-Wood R, Dallimore CM, Whittaker JA. Effect of adriamycin on CFU_{GM} at plasma concentrations found following therapeutic infusions. *Br J Cancer* 1984, **50**, 351–355.
92. Buick RN, Messner HA, Till JE, McCulloch EA. Cytotoxicity of adriamycin and daunorubicin for normal and leukemia progenitor cells of man. *J Natl Cancer Inst* 1979, **62**, 249–255.
93. Ritch PS, Occhipinti SJ, Skramstad KS, *et al.* Increased relative effectiveness of doxorubicin against slowly proliferating sarcoma 180 cells after prolonged drug exposure. *Cancer Treat Rep* 1982, **66**, 1159–1168.
94. Milano G, Cassuto Viguier E, Fischel JL, *et al.* Doxorubicin weekly low dose administration: *in vitro* cytoxicity generated by the typical pharmacokinetic profile. *Eur J Cancer* 1992, **28A**, 1881–1885.
95. Hu XF, Slater A, Wall DM, *et al.* Rapid up-regulation of mdr1 expression by anthracyclines in a classical multidrug-resistant cell line. *Br J Cancer* 1995, **71**, 931–936.
96. Chevillard S, Vielh P, Bastian B, Coppey J. A single 24h contact time with adriamycin provokes the emergence of resistant cells expressing the gp 170 protein. *Anticancer Res* 1992, **12**, 495–500.
97. Lai GM, Chen YN, Mickley LA, Fojo AT, Bates SE. P-glycoprotein expression and schedule dependence of adriamycin cytotoxicity in human colon carcinoma cell lines. *Int J Cancer* 1991, **49**, 696–703.
98. Anderson N, Lokich JJ. Cancer chemotherapy and infusional scheduling. *Oncology Huntingt* 1994, **8**, 99–111.
99. Borden EC, Amato DA, Rosenbaum CH, *et al.* Randomized comparison of three adriamycin regimens for metastatic soft tissue sarcomas. *J Clin Oncol* 1987, **5**, 840–850.
100. Bielack SS, Fuchs N, Bieling P, *et al.* Effect of doxorubicin (DOX) schedule on tumor response and survival in osteosarcoma (OS). Results of sequential trials COSS 86A-C. *Med Pediatr Oncol* 1994, **23**, 176 (Abstract).
101. Lokich JA, Auerbach M, Smith MA, *et al.* A comparative trial of three schedules for single-agent doxorubicin in advanced breast cancer. An aborted investigation. *J Infus Chemo* 1992, **2**, 185–188.
102. Richards MA, Hopwood P, Ramirez AJ, *et al.* Doxorubicin in advanced breast cancer: influence of schedule on response, survival and quality of life. *Eur J Cancer* 1992, **28A**, 1023–1028.
103. Gundersen S, Kvinnsland S, Klepp O, Kvaloy S, Lund E, Host O. Weekly adriamycin versus VAC in advanced breast cancer. A randomized trial. *Eur J Cancer Clin Oncol* 1986, **22**, 1431–1434.
104. Anderson H, Hopwood P, Prendiville J, Radford JA, Thatcher N, Ashcroft L. A randomised study of bolus vs continuous pump infusion of ifosfamide and doxorubicin with oral etoposide for small cell lung cancer. *Br J Cancer* 1993, **67**, 1385–1390.
105. Souhami RL, Rudd R, Ruiz de Elvira MC, *et al.* Randomized trial comparing weekly versus 3-week chemotherapy in small-cell lung cancer: a Cancer Research Campaign trial. *J Clin Oncol* 1994, **12**, 1806–1813.
106. Sculier JP, Paesmans M, Bureau G, *et al.* Multiple-drug weekly chemotherapy versus standard combination regimen in small-cell lung cancer: a phase III randomized study conducted by the European Lung Cancer Working Party. *J Clin Oncol* 1993, **11**, 1858–1865.
107. Casper E, Magill G, Freidrich C, Gaynor J, Hajdu S, Brennan M. Prospective randomized trial of adjuvant adriamycin (A) by bolus (B) vs 72-hour continuous infusion (CI) in patients (PTS) with high grade soft tissue sarcoma (HGS). *Proc Annu Meet Am Soc Clin Oncol* 1989, **8**, A1246.
108. Tierney JF, Mosseri V, Stewart LA, Souhami RL, Parmar MKB. Adjuvant chemotherapy for soft-tissue sarcoma: review and meta-analysis of the published results of randomised clinical trials. *Br J Cancer* 1995, **72**, 469–475.
109. Bieling P, Winkler K, Bielack S, *et al.* Continuous infusion (CI) versus short term infusion (SI) of doxorubicin (DOX) in osteosarcoma. *Proc Annu Meet Am Soc Clin Oncol* 1991, **10**, 308A.
110. Smith MA, Ungerleider RS, Horowitz ME, Simon R. Influence of doxorubicin dose intensity on response and outcome for patients with osteogenic sarcoma and Ewing's sarcoma. *J Natl Cancer Inst* 1991, **83**, 1460–1470.
111. Benjamin RS, Chawla SP, Carrasco CH, *et al.* Preoperative chemotherapy for osteosarcoma with intravenous adriamycin and intra-arterial cisplatinum. *Ann Oncol* 1992, **3**, 3–6.
112. Blomqvist C, Elooma I, Rissanen P, Hietanen P, Nevasaari K, Helle L. Influence of treatment schedule on toxicity and efficacy of cyclophosphamide, epirubicin, and fluorouracil in metastatic breast cancer. A randomized trial comparing weekly and every-4-week administration. *J Clin Oncol* 1993, **11**, 467–473.
113. Twelves CJ, Ramirez AJ, Richards MA, *et al.* A comparison of response, survival and quality of life (QOL) using 2 doxorubicin schedules of equal dose intensity in metastatic breast cancer. *Br J Cancer* 1990, **62**, 498–499.

114. Anderson H, Prendiville J, Thatcher N, Radford JA, Swindell R. A randomised study of intravenous bolus vs continuous infusion of ifosfamide and doxorubicin with oral etoposide for small cell lung cancer. *J Cancer Res Clin Oncol* 1991, **117** (Suppl. IV), S139–S140.
115. Preisler HD, Gessner T, Azarnia N, *et al.* Relationship between plasma adriamycin level and the outcome of remission induction therapy for acute non-lymphocytic leukemia. *Cancer Chemother Pharmacol* 1984, **12**, 125–130.
116. Donohue SM, Boughton BJ. Fractionated anthracycline therapy in acute myeloblastic leukemia in adults. *Cancer Chemother Pharmacol* 1989, **23**, 401–402.
117. Archimbaud E, Anglaret B, Thomas X, *et al.* Continuous-infusion daunorubicin and carboplatin for high-risk acute myeloid leukemia in the elderly. *Leukemia* 1992, **6**, 776–779.
118. Friedenberg WR, Miller HJ, Marx JJ, *et al.* The treatment of older adult patients with acute myeloid leukemia by triple infusion chemotherapy. *Am J Clin Oncol* 1995, **18**, 105–110.
119. Lewis JP, Meyers FJ, Tanaken L. Daunomycin administered by continuous infusion is effective in the treatment of acute non-lymphocytic leukemia. *Br J Haematol* 1985, **61**, 261–265.
120. Janka GE, Harms D, Schwamborn D, *et al.* Daunorubicin-induced cell kill with 1-hour vs. 24-hour infusions: randomized comparison in newly diagnosed children with acute lymphoblastic leukemia. *Proceedings of the XIIth Meeting of the International Society of Hematology*. Vienna, 28 August–3 September 1993.
121. Steinherz PG, Redner A, Steinherz L, Meyers P, Tan C, Heller G. Development of a new intensive therapy for acute lymphoblastic leukemia in children at increased risk of early relapse. The Memorial Sloan-Kettering-New York-II protocol. *Cancer* 1993, **72**, 3120–3130.
122. Shaw PJ, Eden T, Paradisis M. Induction toxicity in acute lymphoblastic leukemia: a comparison of two schedules of daunorubicin administration. *Med Pediatr Oncol* 1995, **24**, 18–22.
123. Sparano JA, Wiernik PH, Leaf A, Dutcher JP. Infusional cyclophosphamide, doxorubicin, and etoposide in relapsed and resistant non-Hodgkin's lymphoma: evidence for a schedule-dependent effect favoring infusional administration of chemotherapy. *J Clin Oncol* 1993, **11**, 1071–1079.
124. Carrion JR, Garcia-Arroyo FR, Salinas P. Infusional chemotherapy (EPOCH) in patients with refractory or relapsed lymphoma. *Am J Clin Oncol* 1995, **18**, 44–46.
125. Slevin ML, Clark PL, Joel SP, *et al.* A randomized trial to evaluate the effect of schedule on the activity of etoposide in small cell lung cancer. *J Clin Oncol* 1989, **7**, 1333–1339.
126. Anderson H, Scarffe JH, Ranson M, *et al.* VAD chemotherapy as remission induction for multiple myeloma. *Br J Cancer* 1995, **71**, 326–330.
127. Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. *N Engl J Med* 1984, **310**, 1353–1356.
128. Browman GP, Belch A, Skillings J, Wilson K, Bergsagel D. Modified adriamycin-vincristine-dexamethasone (m-VAD) in primary refractory and relapsed plasma cell myeloma: an NCI (Canada) pilot study. *Br J Haematol* 1992, **82**, 555–559.
129. Koskela K, Pelliniemi TT, Remes K. VAD regimen in the treatment of resistant multiple myeloma: slow or fast infusion? *Leuk Lymphoma* 1993, **10**, 347–351.