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Retrospective Review of Chemotherapy for Small Cell Lung Cancer in the Elderly: Does the End Justify the Means?

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Between 1978 and 1983, 72 patients aged 70 years or older (median 72, range 70–80) were treated for biopsy-proven, small cell lung cancer (SCLC). Intercurrent disorders were common, including ischaemic heart disease, peripheral vascular disease, chronic airflow limitation and second malignancies. 26 patients (36%) had limited extent of disease, and 46 (64%) had extensive disease. "Intensive" chemotherapy incorporating vincristine, cyclophosphamide and doxorubicin (OCA regimen) was administered to 32 patients [complete response (CR) + partial response (PR) = 84%]; less rigorous regimens (e.g. single agent chemotherapy, planned dose reductions, radiotherapy only) were used in 34 cases (CR + PR = 52%); and 6 received no active treatment. In the intensively treated group, there were 3 treatment-related deaths and 26 episodes of WHO grade 3–4 toxicity. In the less intensively treated group, there were no treatment-induced deaths and only 1 episode of severe toxicity. The overall median survival was 25 weeks (36 weeks for intensive treatment, 16 weeks with less intense treatment). For patients with limited disease only, the median survival in each group was 43 and 26 weeks, respectively. Intensive treatment for elderly patients with small cell lung cancer is associated with substantially increased toxicity and higher response rates than for gentle treatment, but without a major survival benefit.
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INTRODUCTION

THE PROPORTION of the population who will live beyond 70 years is steadily increasing. Currently, 6% of the Australian population are older than 70 years and 37% of newly diagnosed cancers occur in this age group [1, 2]. In the elderly non-institutionalised US population, a 70-year-old may expect, on average, to live 14 years [3]. For a 70-year-old man, the average active life expectancy, defined on the basis of several measures of independence, is 8 years [3].

However, with increasing age, the physiology and organ functions of the body change [2], thus altering the pharmacokinetics and toxicities of cytotoxic agents. There has been considerable controversy regarding the potential benefits and drawbacks of intensive treatment for cancer in the elderly, and it is not clear whether the toxicity of intensive treatment is justified by the level of gain, as measured by reduced cancer-related symptoms or prolongation of life [2].

Because of the design of many clinical trials, including criteria of entry that preclude involvement of patients older than 65–70 years, most series have not reported the outcomes of intensive treatment of elderly patients with small cell lung cancer (SCLC). As a result, there is little published information regarding the results of treatment in this age group. To clarify the issue, we have therefore conducted a retrospective review of all patients aged 70 years or older with SCLC seen at Royal Prince Alfred Hospital, Sydney, between 1978 and 1983, thus allowing a minimum follow-up of 5 years for all patients.

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PATIENTS AND METHODS

All patients aged 70 years or older, with histologically or cytologically confirmed SCLC, diagnosed at this institution between 1978 and 1983 were identified through the Department of Anatomical Pathology and the records of the Departments of Radiation Oncology and Clinical Oncology. Hospital medical records and the files of the NSW Central Cancer Registry were examined.

The indices of the study included age, symptoms and signs at presentation, intercurrent diseases, performance status (as defined by the Eastern Cooperative Oncology Group, ECOG) [4], extent of tumour, type of treatment, tumour response [5], toxicity of treatment [5], sites of relapse, total survival, number of days spent in hospital, and place of death. As this was a retrospective study, no additional formal indices of quality of life were assessed.

The extent of disease was defined as "limited" if staging investigations showed the tumour to be confined to one hemithorax or ipsilateral supraclavicular lymph node, and which could be treated within a single radiotherapy port. Extensive disease was defined by spread beyond these limits. The pattern of toxicity was grouped as "mild" (WHO grades 1–2) or "severe" (grades 3–4).

Each patient underwent the standard assessment procedures of our unit, including history and physical examination, full blood count and biochemical screen (including renal and hepatic function tests). Bronchoscopy, radionucleide bone scans and liver scans were performed in most patients. However, bone marrow biopsy was rarely obtained.

The schedules of treatment are summarised in Table 1.

Table 1. Treatment regimens

Intensive treatments*	
OCA (n = 21)	Vincristine 1.0 mg/m^2; cyclophosphamide 750 mg/m^2; doxorubicin 50 mg/m^2; all intravenously on day 1 (3-weekly)
OCA (n = 2)	+ methotrexate 1 g/m^2 intravenously over 24 h day 1; rolinic acid 15 mg every 6 h × 15 doses; Cycle every 3 weeks
OCA (n = 2)	+ etoposide 60 mg/m^2 intravenously days 1–3 (3-weekly)
OCA (n = 5)	+ cisplatin 60 mg/m^2 intravenously day 1; etoposide 120 mg/m^2 intravenously days 1–3 (3-weekly)
OCA (n = 2)	+ hemibody irradiation (upper +/or lower)
Gentle treatments	
Etoposide (n = 9)	100 mg/m^2 days 1–3 intravenously (3-weekly)
Teniposide (n = 1)	60 mg/m^2 days 1–5 intravenously (3-weekly)
Cytarabine (n = 1)	150 mg/m^2 day intravenously infusion × 3 days (3-weekly)
OCA (low intensity) (n = 8)	Either reduced doses or fewer than 4 treatments intended due to age of patient alone
Radiotherapy (n = 15)	Palliative, to symptomatic sites

* All of these chemotherapy regimens were combined with radiotherapy to the primary site in selected patients.

Patients categorised as receiving "intensive" chemotherapy were treated with vincristine, cyclophosphamide and doxorubicin, and in some instances received additional drugs as shown. These treatment regimens were routinely employed in this Unit over the 5-year survey period. The standard approach included the administration of radiotherapy to patients with limited disease after three cycles of chemotherapy; as noted below, in 6 of 12 eligible patients radiotherapy was not used, at the discretion of the treating clinician (radiotherapy being witheld because of the pattern of summation toxicity seen concurrently in our younger patients). Patients classified as receiving "gentle" treatment included those treated with radiotherapy alone, single agent chemotherapy, or with multi-agent chemotherapy that was initiated at reduced dosage or with a planned reduction to less than four courses. In defining our "intensive" treatment group, we attempted to exclude patients who were, by current standards, suboptimally treated purely because of age.

Survival was calculated from the first day of treatment using Kaplan–Meier analysis [6] on a SPIDA statistical package [7]. Only 1 patient was lost to follow-up, and was censored at the time last known to be alive. Deaths from the toxicity of treatment or from intercurrent disease during treatment were considered as failures of treatment in order to ensure the maximum stringency of assessment of outcome. Similarly, 1 patient, who died 36 weeks after diagnosis, had completed active treatment 2 months previously; he had been reviewed 5 days before death and was noted to be free of disease, but was classified as a failure of treatment (censoring of this case made no difference to any of the statistical assessments).

RESULTS

During the survey period, SCLC was diagnosed in 72 patients aged 70 years or older, comprising 16% of all cases. There were 57 men and 15 women, with a median age of 72 years (range 70–80). The distribution of peformance status is summarised in Table 2. Limited disease (LD) was documented in 26 patients (36%) and extensive disease (ED) in 46 (64%). The histological or cytological diagnosis was pure SCLC in 67 patients (93%) and mixed SCLC and non-small cell cancer in 5 cases. Patients with only non-small cell lung cancer were excluded from the study. Intercurrent illnesses were common (Table 3), with ischaemic heart disease, peripheral vascular disease, chronic airflow limitation, hypertension and second malignancies being the most prevalent problems.

Of the 32 patients who received intensive tretment, 22 (6 LD, 16 ED) had chemotherapy alone and 10 (6 LD, 4 ED) had chemotherapy plus radiotherapy to the primary site. Of the 6 patients with LD treated in the intensive treatment group, only 3 received more than 40 Gy (2.5 Gy per fraction) to the primary site. Gentle treatment was given to 34 patients (13 LD, 21 ED), and 6 patients (8%) received no chemotherapy at all.

Table 2. Patient performance status at presentation

	Treatment					
	None	Gentle		Intensive		
		LD	ED	LD	ED	Total
Performance status *						
0	0	1	4	3	3	11
1	0	4	6	5	8	23
2	3	2	6	3	4	18
3	1	3	3	1	2	10
4	2	2	1	0	3	8
						70

Performance status unknown = 2

* Using the scale of the Eastern Cooperative Oncology Group [12]

LD = limited disease, ED = extensive disease.

Table 3. Intercurrent disorders

Ischaemic heart disease	17
Previous myocardial infarction	11
Cardiac failure	4
Other	2
Peripheral vascular disease	14
Chronic airflow limitation	13
Hypertension	10
Intercurrent malignancies	9
Non-melanomatous skin carcinoma	3
Colon carcinoma	2
Melanoma	1
Squamous carcinoma of lip	1
Squamous carcinoma of vulva	1
Renal carcinoma	1
Arthritis	5
Diabetes mellitis	2
Benign prostatic hypertrophy	2
Cerebrovascular accident	1
Epilepsy	1
Peptic ulcer	1
Pagets disease	1
Silicosis	1
Bladder polyp	1
Renal insufficiency (creatinine > 0.15 mmol/l)	7

Table 4. Response to treatment

Treatment* (n = 66)	Response				
	CR	PR	NC	PD	Unknown
Intensive					
LD (n = 12)	7	4	0	0	1
ED (n = 20)	5	10	2	3	0
Gentle					
LD (n = 13)	3	4	2	4	0
ED (n = 21)	2	8	4	6	1

* 6 patients in the series had no active treatment.
CR = complete response, PR = partial response, NC = no change, PD = progressive disease, LD = limited disease, ED = extensive disease.

The response to chemotherapy is summarised in Table 4. The overall response rate after intensive chemotherapy was 84% (26/31; 95% confidence limits 66–95%; 1 response undocumented). After gentle chemotherapy, response was documented in 52% of cases (17/33; 95% confidence limits 34–70%; 1 undocumented). This difference was statistically significant (P = 0.006, Fisher's exact test). 6 of the 7 patients with LD who achieved complete response after intensive treatment relapsed locally (86%); 4 of these had received radiotherapy to the primary tumour.

3 patients died from the toxicity of treatment (pneumonia while neutropenic; neutropenic sepsis with thrombocytopenic gastrointestinal haemorrhage; gastrointestinal haemorrhage while thrombocytopenic). The pattern of toxicity is summarised in Table 5. Of importance, some patients experienced more than one side-effect at a time. Of the 32 patients treated intensively, 16 did not complete the planned minimum of four

Table 5. Treatment toxicities

	No. of episodes		
	Intensive Treatment	Gentle Treatment	Total
Major * (15 patients)			
Neutropenia	7		7
Nausea and vomiting	4	1	5
Alopecia	4		4
Infection	3		3
Mucositis	2		2
Thrombocytopenia	2		2
Haemorrhage	2		2
Cardiomyopathy	1		1
Cutaneous	1		1
Total	26	1	27
Minor (40 patients)			
Nausea and vomiting	20	14	34
Neutropenia			7
Alopecia	5	2	7
Mucositis	2	2	4
Neuropathy	3		3
Total	37	18	55

* Major toxicity = WHO grades 3–4; minor = WHO grades 1–2 [9].

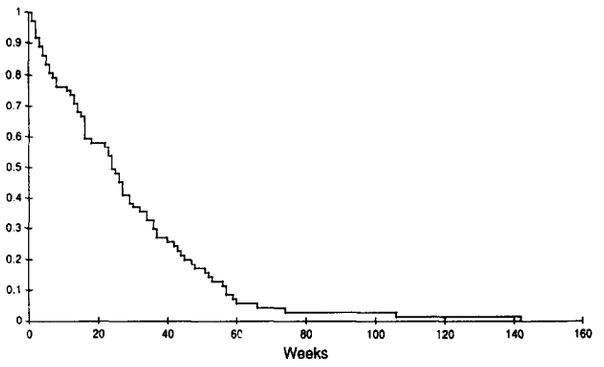

Fig. 1. Overall survival (median survival 25 weeks).

cycles of chemotherapy: 3 refused further treatment, 3 had major toxicity that precluded further treatment, 3 died of toxicity, and 2 died of intercurrent disease (myocardial infarction; cerebrovascular accident), 4 failed to respond to treatment, and 1 patient was lost to follow-up after three cycles of treatment. The median number of days spent hospitalised during treatment was 22, with no significant difference between those treated by intensive or gentle means.

The median survival of the series of 72 patients was 25 weeks (36 weeks with intensive treatment, 16 weeks after gentle treatment and 5 weeks with no active treatment). The median survival for the total group with LD was 34 weeks, while those with ED had a median survival of 23 weeks (logrank P = 0.085). For the 12 patients with LD, the median survival with intensive treatment was 43 weeks, compared wih 26 weeks for the 13 patients who received gentle treatment (P = 0.46). Less than 20% were alive at 1 year, and only 2 patients survived more than 2 years (106 and 142 weeks) (see Figs 1–5).

Death was caused by progressive tumour (65 cases), toxicity of treatment (3), non-cancer coronary artery emblus (1), cerebrovascular accident (1) and undiagnosed sudden death (1). 1 patient was lost to follow up. 49 patients died in hospital, 9 at home, 7 in a hospice, and 3 in nursing homes. The place of death was not documented in four instances.

DISCUSSION

The key issue in the treatment of eldery patients with SCLC is whether the intensive regimens, used routinely in younger patients, yield sufficient benefit to justify the level of toxicity.

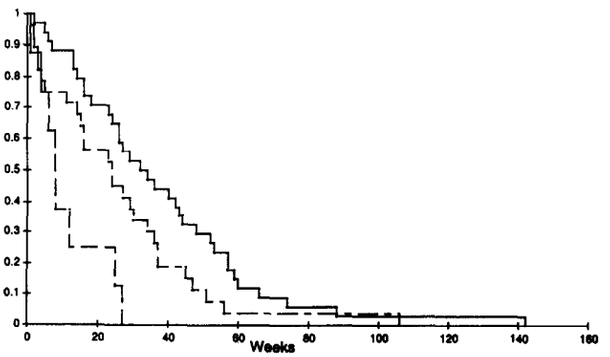

Fig. 2. Survival by performance status at presentation. Median survival for performance status 0 + 1 (——) was 32 weeks, 2 + 3 (---) 24 weeks and 4 (--) 8 weeks. Logrank P = 0.006.

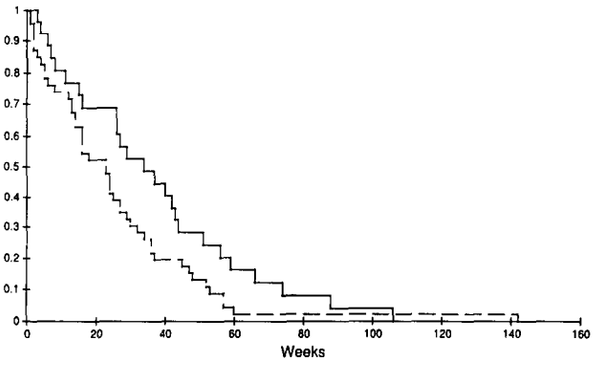

Fig. 3. Survival by disease extent. Median survival for limited disease (——) was 34 weeks and extensive disease (--) 23 weeks. Logrank $P = 0.085$.

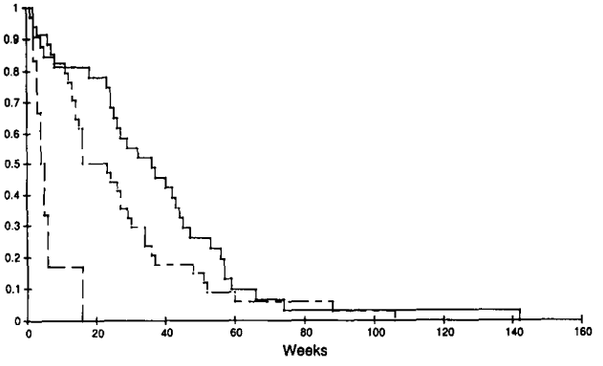

Fig. 4. Survival by treatment group. Medial survival with intensive treatment (——) was 36 weeks, gentle treatment (-·-) 16 weeks and no treatment (--) 5 weeks. Intensive vs. gentle: logrank $P = 0.11$.

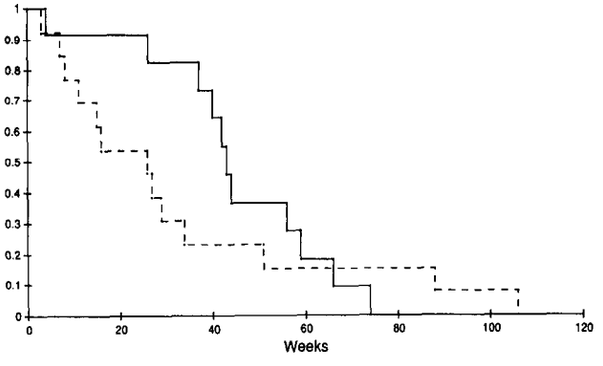

Fig. 5. Survival of patients with limited disease by treatment group. Median survival for intensive treatment (——) was 43 weeks and gentle treatment (-·-) 26 weeks. Logrank $P = 0.46$.

Clamon *et al.* [8] retrospectively studied 24 patients over the age of 70 years with SCLC, revealing a similar pattern of intercurrent disease to our series. After intensive treatment with vincristine, cyclophosphamide and doxorubicin, the median survival in this series was 10 months, with 30% of patients alive at 1 year. The authors concluded that treatment may have been beneficial. However, only 5 patients were able to tolerate treatment without dose reduction.

The Cancer and Leukemia Group B treated 224 patients in a randomised trial that compared three combination regimens against single agent cyclophosphamide [9]. 28 patients were aged 70 years or older. This group had a lower proportion achieving complete remission, especially if they had LD. Furthermore, none of the patients with LD in the old age group survived more than 2 years, compared with 15% of the younger cohort. It was concluded that age greater than 70 years was a significant adverse survival factor after adjustment for risk [9].

By contrast, Poplin *et al.* [10] reviewed 223 patients treated intensively with etoposide, cyclophosphamide and doxorubicin for SCLC, of whom 49 were older than 64 years. The older patients had similar objective response rates to the rest of the cohort, but with more myelotoxicity and a statistical trend towards increased treatment related deaths. However, their overall pattern of survival was similar to the rest of the group.

In our series, major toxicity was confined to the intensive treatment group. Myelosuppression, which represented 33% of the major toxicities, was a significant factor in the 3 treatment-related deaths (9% of the intensive treatment group). It is likely that an even higher morbidity would have been experienced with a more aggressive application of the planned treatment intensity. In fact, we were only able to administer four or more cycles of chemotherapy to 50% of the patients allocated to intensive treatment, as outlined previously. Although the criticism could be raised that this did not constitute truly "intensive" treatment by current standards, the level of toxicity was significant and a clear attempt was made to use an approach considered to be intensive at the time of the study. Furthermore, there is little objective evidence to prove that high dose, intensive treatment (by current standards) affords a benefit in terms of survival (the principal endpoint of our study).

Offsetting to some extent the level of toxicity, we have shown a higher rate of objective reponse to the intensive treatment, as compared to gentle therapy. At first glance, the absence of a statistically significant difference in survival between these two groups could have been due to the small numbers of patients in the series. Furthermore, we recognise that the inclusion into the "gentle" category of patients treated with a planned protocol of less than four cycles of OCA might have biased the study. In addition, the relatively conservative doses of radiotherapy to the primary tumour could also have contributed to bias.

However, upon reordering the data to classify all patients treated with OCA in the intensive group, no impact on survival was demonstrated (data not shown). Furthermore, in the broader context, one must question the utility of the intensive OCA regimen in elderly patients, given the fact that less than 20% were alive at 1 year and only 2 patients survived beyond 2 years. We conclude that the toxicity of OCA intensive chemotherapy in the elderly is not justified by the pattern of survival, and that other approaches should be sought to improve the outcomes of treatment. To this end, in an attempt to ameliorate the toxicity of treatment, we have assessed regimens based on the combination of etoposide and carboplatin in patients with SCLC [11, 12] and are now evaluating the impact of these regimens on the treatment of SCLC in the elderly.

1. Giles GG, Armstrong BK, Smith CR. *Cancer in Australia*, National Cancer Statistics Clearing House Scientific Publication, Melbourne, 1982, 73, 106.
2. Raghavan D, Findlay MP, McNeil E. Cancer in the elderly. In: Peckham MJ, Pinedo H, Veronese U. (eds). *Oxford Textbook of Oncology*, Oxford, Oxford University Press, (in press).

3. Katz S, Branch LG, Branson MH, *et al.* Active life expectancy. *N Engl J Med* 1982, **309**, 1218–1224.
4. Zubrod CG, Schneiderman M. Frei E, *et al.* Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. *J Chron Dis* 1960, **11**, 7–12.
5. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
6. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
7. Lunn D, McNeil DR. *SPIDA Users Manual.* Sydney, Southwood Press, 1988.
8. Clamon GH, Audeh MW, Pinnick S. Small cell lung carcinoma in the elderly. *J Am Geriatr Soc* 1982, **30**, 299–302.
9. Maurer LH, Pajak TF. Prognostic factors in small cell carcinoma of the lung: a Cancer and Leukemia Group B study. *Cancer Treat Rep* 1981, **65**, 767–774.
10. Poplin E, Thompson B, Whitacre M, Aisner J. Small cell carcinoma of the lung: influence of age on treatment outcome. *Cancer Treat Rep* 1987, **71**, 291–296.
11. Bishop JF, Raghavan D, Stuart-Harris R, *et al.* Carboplatin (CBDCA, JM-8) and VP16-213 in previously untreated patients with small cell lung cancer. *J Clin Oncol* 1987, **5**, 1574–1578.
12. Bishop JF, Kefford RF, Raghavan D, *et al.* Etoposide, carboplatin, cyclophosphamide and vincristine (ECCO) in previously untreated patients with small cell lung cancer. *Cancer Chemother Pharmacol* 1990, **25**, 367–370.

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Early Cardiac Toxicity of 4′-Iodo-4′-deoxydoxorubicin

Fabrizio Villani, Milena Galimberti and Roberto Comazzi

4′-iodo-4′-deoxydoxorubicin was administered intravenously to 35 patients with advanced malignant neoplasms. The doses were escalated as follows: 2, 4, 6, 7, 10, 14, 19, 26, 52, 70, 80 and 90 mg/m². Myocardial function was assessed by Holter monitoring and echocardiography. The prevalence of arrhythmias that could be attributed to the drug in the 24 h following infusion was 14.3% (supraventricular) and 10.6% (ventricular). Echocardiographic heart function variables were unchanged at 24 h and 21 days from drug injection. The data indicate the absence of significant, acute cardiotoxic effects of 4′-iodo-4′-deoxydoxorubicin.
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INTRODUCTION

DELAYED CARDIOTOXICITY represents the major limitation to the use of anthracyclines in long-term treatment. Moreover, a transient decrease in myocardial contractility and cardiac arrhythmias, mainly represented by ventricular premature beats and repolarisation abnormalities, have been reported after anthracycline administration [1–3]. 4′-iodo-4′-deoxydoxorubicin (I-DOX) is an analogue of doxorubicin that is modified in the amino sugar, where the hydroxyl group at C4′ has been substituted with an iodine atom. The novel anthracycline has shown interesting antineoplastic activity. In fact, it was found more potent than doxorubicin on several murine and human tumour cell lines [4–8]. In preliminary tests performed in mice and rats, the analogue showed consistently less cardiotoxic activity than doxorubicin [7–9].

We report the results of an evaluation of cardiac function and cardiac electrical activity in a phase I trial which included 35 patients with metastatic carcinoma. The purpose of the trial was to determine, on the basis of a pharmacokinetically guided dose escalation, the maximum tolerated dose [10].

PATIENTS AND METHODS

The study was conducted on 35 patients suffering from different kinds of cancer: 10 gastrointestinal carcinomas, 5 kidney carcinomas, 5 non-small-cell lung carcinomas, 5 unknown primary carcinomas, 2 hepatocellular carcinomas, 2 breast cancers, 2 melanomas, 2 sarcomas, 1 ovarian carcinoma, and 1 non-Hodgkin lymphoma. 24 patients were men and 11 women; their median age was 47 years (range, 16–75). The patients were all in good general condition (median Karnofsky performance status, 90; range, 80–100). 4 patients had been previously treated with very low doses of anthracyclines (doxorubicin, median dose 180 mg/m²; range, 90–260) and 17 patients with other anticancer agents.

Patients with electrocardiogram (ECG) abnormalities of conduction and/or severe repolarisation alterations were excluded from the study. Moreover, patients with a previous history of heart disease or under treatment with diuretics, beta blockers, calcium antagonists, nitrates or vasodilators were also excluded from the study.

Evaluation of left ventricular contractility

Left ventricular M-mode echocardiogram, phonocardiogram, indirect carotid pulse tracing and blood pressure measurements were obtained simultaneously before and 24 h and 21 days after I-DOX injection. Peak systolic and diastolic blood pressure measurements were performed with a Dinamap 845 vital signs monitor (Critikon, Tampa, Florida). The percentage of fractional shortening of left ventricular minor axis (MAS%), the relative velocity of contraction (RVC), and the relation of left ventricular end-systolic wall stress (σ_{cs})/MAS% were used as indices of left ventricular contractility. RVC was calculated as previously described [11]. The relationship between left

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