Doxorubicin Cardiomyopathy in Lung Cancer Patients

Pages with reference to book, From 142 To 145

Tariq Siddiqui (Department of Oncology and Hematology, University of Florida Health Sciences, Jacksonville, FLA 32209, USA.)

Ikram A. Bumev (Department of Medicine, Aga Khan University Hospital, Karachi.)

Abstract

Doxorubicm is cardiotoxic and its use must be monitored carefully. Incidence of refractory cardiac failure is shown to increase once the cumulative dose exeeds 450 mg/m^2, However, significant decline of ejection fraction (EF) may occur even at lower dose levels. EF was monitored using Multigated Radionuclide Angiography (MUGA) scan of all consecutive lung cancer patients, treated with Doxorubicin based regimens. Thirteen of 82 patients showed a significant (more than 15%) decline of left ventricular EF, The dose of doxorubicin producing this decline ranged between 91-180 mg/m^2. Actual decline in EF ranged between 16-45%. Only 5 of 13 patients developed symptoms attributable to the cardiac disease. Doxorubicin can alter EF significantly in lung cancer patients at levels well below which are considered 'safe', The reason for massive decline in ejection fraction in these patients has been hypothesized (JPMA 48:142, 1998).

Introduction

Doxombicin belongs to the anthracycline group of antibiotics which are widely used in cancer chemotherapy.

Unfortunately, doxorubicin, like all other anthracycline compounds is cardiotoxic and must be monitored carefully when used. Thus, the clinical decision to use doxorubicin includes a balancing of the known risk factors which may enhance myocardial toxicity with its therapeutic efficacy. The factors which enhance the side effects of doxorubicin include prior cardiac disease, hypertension, previous chemotherapy, mediastinal irradication and most importantly, the total cumulative dose of doxorubicin (or other anthracyclines) used[1-3]. Long clinical experience has shown that a total cumulative dose of up to 450-550 mg/m^2 is generally "safe"[2]. There is great individual variability to doxombicin related cardiotoxicity. Some patients may tolerate doxorubicin dosages far in excess of the so called safe range, whereas, others may have difficulty with much lesser cumulative doses. Unfortunately, however, it is not possible to piedict which patient will developcardiotoxicity and at what dose levels[2,4]. Thus, the cuntnt clinical practice includes not only an awaxeness of iisk factors which predispose toward the development of cardiotoxicity, but also clinical and laboratoiy monitoring of ventricular function during doxorubicin adminisinition. The latter includes a number of investigations including an endomyocanlial biopsy and the multigated radionucide angiography (MUGA) scan. Of these, the MUGA scan is widely used because of its technical ease, reproducibility and accuracy in determining the ejection fraction. It is currently the investigation of choice to monitor doxorubicin cardiotoxicity[2,5].

At the Universit Hospital of Jacksonville, Florida, a large number of patients are seen each year with lung cancer. Some of these cases are treated with combination chemotherapy regimens containing doxombicin. In reviewing this experience, we have been impressed with the observation that patients suffering from lung cancer who developed a decline of ejection fraction have done so at a much lower dosage than are the usual "safe" lower cumulative dosages generally recommended. This paper is a compilation of these observations which suggest greater caution when doxombicin is used in lung cancer patients.

Patients and Methods

Patients suffering from lung cancer, both non-small cell and small cell carcinoma who received doxorubicin based chemotherapy were reviewed. Over a three year period, 82 patients were treated at the University Hospial of Jacksonville, Florida. Of these, 13 patients were found to have an objective decline of left ventricular function. All patients were followed clinically for signs of congestive cardiac failure. This included bibasilar crepitations not attributable to the primaly disease and an S3 gallop rhythm. Objective determination of left ventricular function was carried out by the MUGA scan. The MUGA scan was done on a periodic basis. The periodicity was decided both clinical and routinely i.e., every 3-4 cycles. The MUGA scanwere done using the following procedure: Two or three mg of stannous pyrophosphate was injected intravenously. Twenty minutes later, 25 m Ci of 99 Tc pertechnate was mixed with 10 cc of blood in ACD solution. After 15 minutes of incubation, the tagged red cells were injected intravenously. A composite gate of 600 beats (using standard beat rejection analysis) or a minimum of 2 million counts was obtained. The images were obtained in. the left anterior oblique and left posterior oblique position, on a GE starcan and a LEAP Collimator. The left ventricular ejection fraction was finally processed.

Results

Eleven out of thirteen patients were men and only two were women. The patients' ages ranged between 49 and 67 years with a median age of 59 years. Five patients had small cell carcinoma (4 limited stage and I extensive stage). Eight patients suffered from non-small cell carcinoma (5 limited stage and 3 extensive stage). All thirteen patients received doxombicin, etoposide and cisplatin including four who received in addition cytoxan, CCNU, methotrexate and vincnstine. Risk factors for the development of doxombicin cardiomyopathy included hypertension in 2 cases and 4500 cGy and 5100 cGy radiation therapy in two other patients. No obvious risk factor could be identified in any other case. Baseline ejection fraction (prior to the initiation of chemotherapy) ranged between 50-62%(55.4±l .2). The dose of doxorubicin ranged between 9 1-180 mg/rn, with an average of 143 mg/rn2. As soon as decline of the left ventricular ejection fraction was detected, doxombicin was deleted from the, chernotherapeutic regimen. The left ventricular ejection fraction after doxorubicin administration ranged between 29% to 45% (40.1±1.5). By the time the left ventricular ejection fractions had declined, only 5/13 cases had developed symptoms attributable to cardiac disease, Four out of five cases had an S3 gallop rhythm on cardiac auscultation. Four patients had cardiornegaly including one who developed pulmonary oedema. The average decline of ejection fraction of symptomatic patients was 25% of the baseline. Eight asyrnptomatic cases had a decline of ejection fraction which averaged 27%. None of these patients had either cardiomegaly or symptoms whichcould be attributed to cardiac dysfunction. A summary of the clinical findings is presented in Tables land II.

Table I.

No.	Age	Sex	Total doxorubicin dose mg/m^2	Histology (Carcinoma)	Risk	Attributed Cardiovascular signs and symptoms	Chest X-ray findings
1	60	M	138	Adeno Ca	None	None	No cardiomegaly
2	60	M	171	Small cell Ca	None	None	No cardiomegaly
3	61	M	91	Small cell Ca	Chest Radiation 5100 cGy	SOB Tachycardia	No cardiomegaly
4	59	F	106	Squamous cell Ca	Old stroke Hypertension	None	No cardiomegaly
5	64	M	157	Squamous cell Ca	None	PND	No cardioegaly
6	65	M	150	Squamous cell Ca	None	S3 gallop	Cardiomegaly
7	49	M	168	Small cell Ca	Hypertension	SOB S3 gallop	Cardiomegaly
8	52	M	144	Adeno Ca	None	None	No cardiomegaly
9	65	M	150	Small cell Ca	None	None	No cardiomegaly
10	52	M	180	Adeno Ca	None	None	No cardiomegaly
11	60	M	100	Small cell Ca	None	None	No cardiomegaly
12	67	M	160	Large cell Ca	None	SOB S3 gallop	Cardiomegaly and pulmonary oedema
13	61	F	150	Adeno Ca	Chest Radiation 4500 cGy	S3 gallob, heart fail	Cardiomegaly

SOB = Shortness of breath
PND = Paroxysmal Nocturnal dyspnoea.

Table II.

Case #	Persent baseline ejection fraction	Percent post doxorubic in ejection fraction	Percent decline	Comments
1	56	41	27	Lived for 24 months following cardiomyopathy
2	53	29	45	Died due to lung cancer after 6 months
3	62	41	34	Died due to lung cancer after 8 months
4	57	42	26	Lost to follow up
5	50	42	16	Survived 24 months
6	50	42	16	Survived 11 months
7	60	40	34	Lost to follow up
8	58	45	23	Died in 9 months
9	58	47	19	Died in 6 months
10	61	45	26	At last follow up alive at 5 months
11	50	30	40	Status unknown
12	55	40	27	Status unknown
13	50	38	24	Died 6 months, 1 month after cardiomyopathy.

Discussion

Doxorubicin is a very useful chemotherapeutic agent and it is an effective therapy for a number of malignant conditions. Some of these include tumors of the lung and breast, lymphomas and certain leukemias. Unfortunately, a major factor which limits the use of doxorubicin is its myocardial toxicity[2]. Recently cardio protective agents such as ICRF-187 have been released for concomitant use with anthracyclines and some degree of rnyocardial4rotection may. be afforded by such therapeutic maneuvers[2,6].

Unfortunately for patients undertaking doxorubicin based chemotherapy, cardiotoxicity is unpredictable and may be severe leading ultimately to patient's deathfrom congestive cardiac failure[8] . It is therefore, necessary for the treating physician to keep in mind a number of risk factors including the total dosage of doxorubicin and some of these conditions such as prior cardiac disease, hypertension, mediastinal irradiation, patients older than 70 years and diabetes mellitus[1-3].

Doxorubicin related cardiac damage is a spectrum of changes and much of what we know about it is due to a retrospective examination of data. It is not an all or none phenomenon. When endomyocardial biopsy is performed during doxorubicin therapy some histopathological damage can be demonstrated[2,9]. Some patients may develop cardiac arrhythmias, durign and after infusion of doxorubicin, while others develop congestive cardiac failure irreversibly. Only a very small proportion have been reported to show clinical recovery[10,11]. Nevertheless for the vast majority of cases the onset of cardiac damage leading to cardiac dilation and failure is an ominous development. The overall incidence of clinical congestive heart failure is of the order of 7-15% when the cumulative dose of doxorubicin reaches up to 450-550 mg/m^2. The incidence of congestive heart failure rises very steeply if this dose limit is exceeded. Some patients develop clinical myocardial toxicity at considerably lower doses and there is no way to predict as to who will do so. Once cardiac dilation and failure sets in, therapeutic measures are those employed for the treatment of congestive heart failure.

In our series of patients, 13 out of 82 cases developed a significant (more than 15%) decline of ejection fraction. The decline occurred at an average dose which was much lower than the "safe" cumulative dose of 450-550 mg/m^2. It is surprising that only 6 of the thirteen cases were symptomatic even with a decline of ejection fraction of 25%, while among the asymptornatic patients the decline was on an average27%. This is clearly not a significant difference. No evidence of congestive cardiac failure was observed in the asymptomatic group of patients despite of the fact that some patients had large ejection fraction declines (patients 2 and 11) of the order of 40% and 45% respectively. Nevertheless, the lack of relationship between the extent of ejection fraction decline and clinical symptornatology is well known[5,9].

The reasons for a decline of the left ventricular ejection fraction in our own patients needs to be hypothesized. It is possible that the factors known to cause lung cancer, for example, cigarette smoke may also cause subclinical myocardial damage which is easily unmasked by myocardial toxicity of doxorubicin. Pulmonary hypertension induced by chronic hypoxia may be a major cause for fibronectin and collagen accumulation leading to diastolic dysfunction[12].

Furthermore, lung cancer patients may also suffer from chronic pulmonary disease. The latter may place an additional burden on the right ventricle due to high pulmonary pressures, thus predisposing both the right and left heart to damage and unpredictable consequences[12]. Biochemically, it is believed that free radical damage is the cause of doxorubicin cardiomyopathy and the free oxygen radicals alongwith Femc -doxorubicin complexes play a significant role[2,12,13]. Whether lung cancer patients are excessively sensitive to the effect of anthracycines needs further confirmation. It is obvious that this study has limitations and is retrospective. Nevertheless, the decline of ejection fraction observed at much lower doses of doxorubicin (on an average 143 mg/m^2) is significant and needs further evaluation.

Acknowledgements

Our thanks are due to Mr. Athar H. Khan for typing the manuscnpt.

References

1. Von.Hoff. D.D.. Layard, MW.. Basa, P. et al. Risk factors for doxorubicin inducedcongestivehcartfailure. Ann. Intern. Med., 1979;91,710-17.
2. Speyer, J.L. and Freedman, R. Cardiac complications; editors Abeloff M.D.. Armitage, JO., Lichter, AS. et al. Clinical Oncology. New York, Edinburgh. London, Melbourne, Tokyo, Churchill Livingstone, 1995. pp. 810-814.
3. Orditura, M.. De-Vita, F., Ciararnella, F. et al. Anthracyclinc induced cardiotoxicity. Ann. Italian Med., 1994;9:243.248.
4. Von-Hoff, D.D.. Rozeneweing, M., Layard. M. et al. Daunomycin induced cardiotoxicity in chidren and adults. A review of 10 cases. Am. J. Med., 1977;62:200.208
5. Schwatz, R.G., Mc-Kenzie, WB., Alexander, J. eta!. Congestiveheartfailureand left ventricular dysfdnction complicating doxorubicin therapy: a seven year experience using serial radionuclideangiocardiography. Am.J. Med., 1987;82: 1109-18.
6. Green, M.D., Alderton, P., Sobol, M.M. et al. ICRF-187 (ADR 529): Cardioprotection against anthracycline induced cardiotoxicity clinical and preclinicat studics. Cancer Treat Rep.. 1991 ;58: 101-17.
7. Alderton, P.M., Gross, J. and Green, M.D. Comparative study of Doxorubicin mitoxantrone, epirubicin in combination with ICRF-1 87 (ADR 529) in a chronic cardiotoxicity animal model. Cancer, Res., 1992;52: 194.201,
8. Moreb, J.S. and Oblon. D.J., Outcome of clinical congestive heart failure induced by anthracycline chcmotherapy. Cancer, 1992;70:2637-41.
9. Billingham. ME., Mason. J.W., Bristow, M.R. et al. Anthracycline cardiomyopathy monitored by morphologic changes. Cancer Treat. Rep.. 1978;62:865-72.
10. Steinherz, L.J., Steinherz, PG. and Tan. C. Cardiac failure and dysrythmias 6-19 years after anthracyclinc therapy. A series of 15 patients. Med. Pediatr. Oncol., 1995;24:352-61.
11. Saini. 3., Rich, M.W. and Lyss, A.P. Reversibility of severe left ventricular dysfunction due to doxorubicin cardiomyopathy. Report of three cases. Ann. Intern. Med., 1987;106:814-16.
12. Xuy.Shiraishi, K., Mori, M. and Motomiya, M. Changes in fibronectin in the right and left ventricles of rats exposed to chronic normobaric hypoxia. Tohoku 3. Exp. Med., 1992;168:573-82.
13. Monti. E., Prosperi. E., Supino, R. et a!. Free radical dependent DNA lesions are involved in the delayed cardiotoxicity induced by adriamycin in the rat. Anticancer Res., 1995;15:193-97.