Original Research Article

Comparison of standard short infusion versus prolonged infusion of Doxorubicin in relation to its cardiotoxicity in South Indian population

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ABSTRACT

Background: Anthracycline is one of the commonly used chemotherapeutic agents in the treatment of malignancies and their efficacy is undermined by potential life-threatening cardiotoxicity. The aim of this study is to compare the cardiotoxicity in patients receiving standard short infusion (15-30 minutes) versus prolonged infusion (6 hours) of doxorubicin in the study group.
Methods: In this study 80 patients who were planned for treatment with Doxorubicin >200 mg/m^2 were included in this study and they were randomly allotted to either of the treatment group. Each patient was assessed clinically (History, Pulse rate, Blood pressure) along with ECG ,ECHO prior to initiation of chemotherapy, after completion of 200 mg/m^2 of Doxorubicin, 3 months and 6 months after chemotherapy.
Results: There were 40 patients in each group, and they received a total of 384 cycles of Doxorubicin containing regimens according to respective protocols. The median number of cycles was four (range four to six cycles). The mean cumulative dose of doxorubicin was 271.5 mg/m^2 in the group which received standard short infusion and 264 mg/m^2 in the group which received the drug by prolonged infusion. However, none of the patients developed any cardiac symptoms during or after the planned chemotherapy nor was there a drop in ejection fraction on serial ECHO.
Conclusions: There was no benefit of prolonged infusion of doxorubicin as compared to the standard rapid infusion in terms of doxorubicin induced cardiotoxicity. At present, standard rapid infusion is the best option.

Keywords: Cardiotoxicity, Doxorubicin, ECHO, Infusion

INTRODUCTION

Anthracycline is one of the commonly used chemotherapeutic agents in the treatment of a wide spectrum of haematological malignancies and solid tumours. However, their efficacy is undermined by potential life-threatening cardiotoxicity.[1]

Anthracycline induced cardiotoxicity is potentiated when the cumulative dose of doxorubicin exceeds 300 mg/m^2.

Symptomatic heart failure is rare with cumulative dose of 240 mg/m^2. However asymptomatic cardiac toxicity is seen even with these cumulative doses as noted. In the North Central Cancer Treatment Group (NCCTG) N9831 trial, after four cycles of anthracycline-containing chemotherapy, 8.5% of 2,992 breast cancer patients had an asymptomatic left-ventricular ejection fraction (LVEF) decline ≥10% but <15% compared with baseline, and 5.0% had an asymptomatic decline >15% or ≤15% to below the lower limit of normal.[2]

According to the time of onset, cardiotoxicities are classified into:

- Acute- occurring after a single dose, or a single course, of anthracyclines, with onset of clinical manifestations within two weeks from the end of treatment.
- Early onset chronic- developing within 6 months -1 year. This is the most frequent and clinically relevant form of cardiotoxicity, usually presenting as a dilated and hypokinetic cardiomyopathy leading to heart failure (HF) .
- Late onset chronic- developing years, or even decades, after the end of chemotherapy.[3]

Early-onset cardiotoxicity occurs within 1 year after anthracycline treatment. Patients may develop ECG changes, left-ventricular dysfunction, and symptoms of clinical heart failure. The peak time for the appearance of symptoms of heart failure is 3 months after the last anthracycline dose, and mortality in these patients is quite high. Late-onset cardiotoxicity occurs more than 1 year after completion of anthracycline treatment. The late toxicity is a major concern in clinical scenarios where anthracyclines are used as part of a curative or adjuvant regimen-for example, in patients with breast cancer. Patients can be asymptomatic initially, and ventricular dysfunction, heart failure, and arrhythmias may occur later, even decades after the discontinuation of anthracycline therapy.[2]

Anthracyclines generate oxygen-derived free radicals using iron as a co-factor and the mitochondrial respiratory chain and most available evidence suggests that myocyte apoptosis is related to increased oxidative stress caused by these processes.[4]

Irrespective of the regimen in which it was included, it was found that the slow 6 hour infusion of Doxorubicin was associated with significantly lower cardiotoxicity than the standard short infusion.[5]

There are no major studies done in our population regarding the reduced cardiotoxicity with prolonged infusion of anthracyclines. All previous trials have used higher dose of anthracyclines and there are no studies to assess the incidence of cardiotoxicity in lesser doses of anthracyclines (200-400 mg/m^2). The present study has been undertaken to compare the standard short infusion (15 minutes) and prolonged infusion (6 hours) of doxorubicin in relation to anthracycline induced cardiotoxicity in patients receiving doxorubicin >200 mg/m^2 in South Indian population.

METHODS

In this study 80 patients with any malignancy presenting to the Department of Medical Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore between January 2016 to June 2017 and who were to

receive Doxorubicin >200 mg/m^2 as part of treatment protocol were included in the study. Patients who were between 18 years and 70 years with any malignancy who will receive >200 mg/m^2 of Doxorubicin as part of the treatment protocol were included in the study. Patients with history of valvular or coronary cardiac diseases, prior exposure to anthracyclines, prior exposure to irradiation to the mediastinum, patient with LVEF <55 % in the baseline ECHO were excluded from the study.

A standard proforma was used to collect patient related data for the study and informed consent was obtained from all patients. Patients who would receive Doxorubicin >200 mg/m^2 as part of treatment protocol were randomly allocated to either of the treatment group i.e. standard short infusion (over 15-30 minutes) and prolonged infusion (6 hours). Prolonged infusion were given through a central line access. Demographic details of these patients were entered in the proforma.

Each patient was assessed clinically (History, Pulse rate, Blood pressure) along with ECG and ECHO prior to initiation of chemotherapy, after completion of 200 mg/m^2 of Doxorubicin, 3 months and 6 months after chemotherapy. Patients were observed for developments of signs and symptoms of CHF, cardiomyopathy characterized by decrease in the LVEF that was either global or more severe in the septum, decline in the LVEF of at least 5% to less than 55% with signs or symptoms of CHF, or a decline in LVEF of at least 10%, to below 55% without signs or symptoms which would suggest cardiotoxicity.

Inclusion criteria

- Age more than 18 years and less than 70 years.
- Patients with any malignancy who will receive >200 mg/m^2 of Doxorubicin as part of the treatment protocol.

Exclusion criteria

- History of valvular or coronary cardiac diseases.
- Prior exposure to anthracyclines.
- Prior exposure to irradiation to the mediastinum.
- Patient with LVEF <55 % in the baseline ECHO

Statistical analysis

The Statistical software namely SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. Descriptive and inferential statistical analysis has been carried out in the present study.

Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. The following

assumptions on data were made. Assumptions include that dependent variables should be normally distributed, samples drawn from the population should be random and that cases of the samples should be independent.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. Fisher Exact test was used when cell samples are very small.[6-9]

RESULTS

A total number of 80 patients with any malignancy presenting to the Department of Medical Oncology, Vydehi Institute of Medical Sciences, Bangalore who received Doxorubicin >200 mg/m^2 as part of treatment protocol were recruited from January 2016 to June 2017 for this study.

The patients were selected according to the inclusion and exclusion criteria as mentioned earlier. Before including the patient in the study a detailed consent was taken from the patient. Patients were then randomized to either the prolonged infusion group or standard short infusion using the chit method. All demographic details were noted in the proforma along with investigations carried out initially and those repeated as mentioned earlier.

There were 40 patients in each group and they received a total of 384 cycles of Doxorubicin containing regimens according to respective protocols. Each patient was assessed clinically (History, Pulse rate, Blood pressure) along with ECG ,ECHO and NT-pro-BNP levels prior to initiation of chemotherapy, after completion of 200 mg/m^2 of Doxorubicin, 3 months and 6 months after chemotherapy.

In authors study the age range of patients included was between 18 years and 70 years of age. The mean age of the patients was 44.34 years. Data on the age distribution of patients included in the study is shown in (Table 1 and Figure 1).

Table 1: Age distribution of patients studied.

Age in years	Duration of Infusion		Total
	15 min	6 hours	
20-30	8(20%)	7(17.5%)	15(18.8%)
31-40	8(20%)	6(15%)	14(17.5%)
41-50	10(25%)	17(42.5%)	27(33.8%)
51-60	9(22.5%)	7(17.5%)	16(20%)
61-70	5(12.5%)	3(7.5%)	8(10%)
Total	40(100%)	40(100%)	80(100%)
Mean±SD	44.60±12.18	44.08±11.88	44.34±11.96

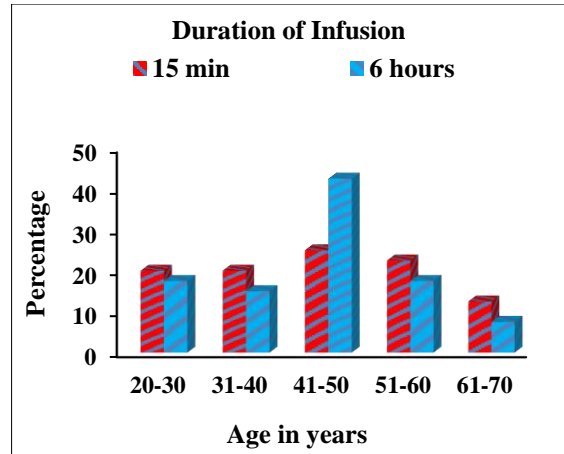p=0.846, Not significant, Student t-test

Figure 1: Age distribution of patients studied.

Most of the patients were between the age group of 31 years to 50 years. A total of 57 females and 23 males were included in the study, distributed among the two groups based on duration of infusion of Doxorubicin as depicted in (Table 2, Figure 2 and Figure 3).

Table 2: Gender distribution of patients studied.

Gender	Duration of Infusion		Total
	15 min	6 hours	
Female	27(67.5%)	30(75%)	57(71.3%)
Male	13(32.5%)	10(25%)	23(28.8%)
Total	40(100%)	40(100%)	80(100%)

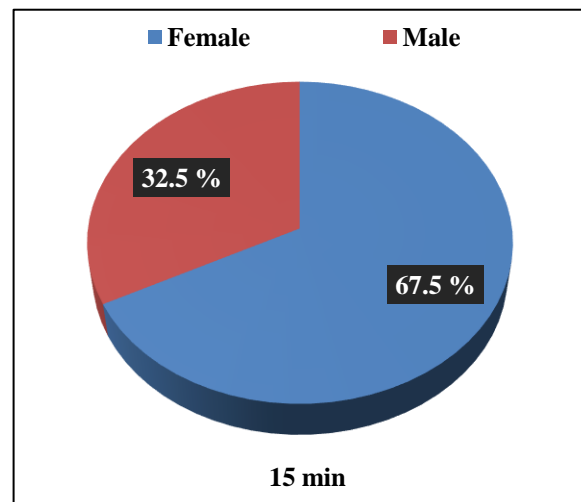p=0.459, Not significant, Chi-Square test

Figure 2: Gender distribution of patients studied in 15 min infusion arm.

Among the study population of 80 patients, only 11 patients had history of co-morbid conditions which included 6 hypertensive patients, 4 patients with diabetes mellitus and one patient with Congenital heart Disease-Atrial Septal Defect- Post surgical closure.
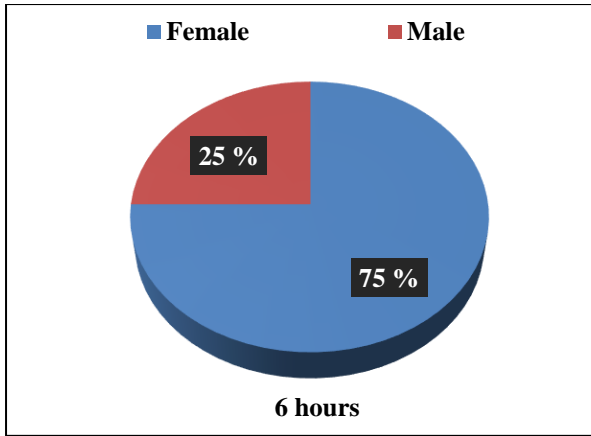
Figure 3: Gender distribution of patients studied in 6 hours infusion arm.

All these patients were on regular medication for these respective illnesses. Table 3 gives the mean values of Height, Weight and BSA of the study population and (Figure 4) gives distribution of BSA in the two groups studied.

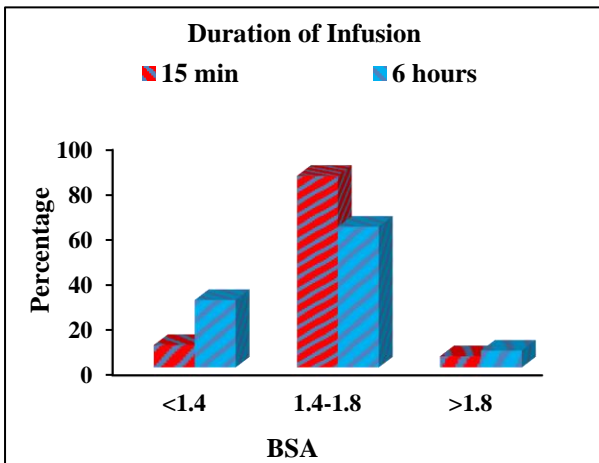Average height was 157.16 cm and average weight was 55.91 kg in the study population of 80 patients.

Figure 4: BSA distribution in two groups of patients studied.

Table 4: Stage distribution in two groups of patients studied.

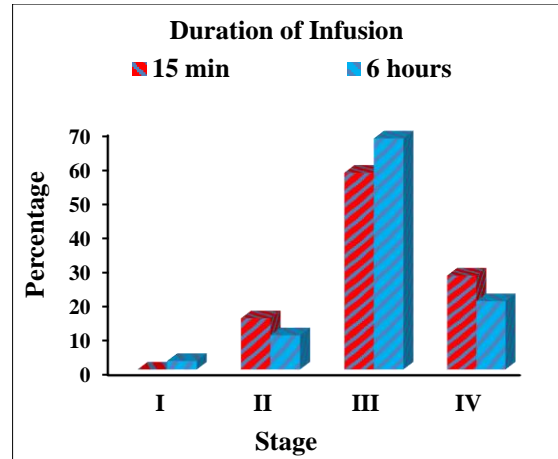| Stage	Duration of Infusion		Total
	15 min	**6 hours**	
I	0(0%)	1(2.5%)	1(1.3%)
II	6(15%)	4(10%)	10(12.5%)
III	23(57.5%)	27(67.5%)	50(62.5%)
IV	11(27.5%)	8(20%)	19(23.8%)
Total	40(100%)	40(100%)	80(100%)
p=0.566, Not Significant, Fisher Exact Test			

Figure 5: Stage distribution in two groups of patients studied.

In this study majority of the patients were Stage III accounting to almost 62.6% of the total study population. There were around 19 patients with Stage IV disease which was 23.8%. The Stage distribution of the study population in each of the groups is mentioned in (Table 4 and Figure 5). The maximum number of patients were carcinoma breast patients constituting almost 60 % of the total study population. The next common diagnosis was Non Hodgkins Lymphoma. The details regarding the diagnosis distribution is mentioned below in (Table 5 and Figure 6).

Details regarding the Doxorubicin containing chemotherapy regimens used are mentioned below in (Table 6). Since majority of the patients included in our study were carcinoma breast patients, the most used chemotherapy regimen was AC (Doxorubicin and Cyclophosphamide). The median number of cycles is four (range four to six cycles) as seen in (Table 7 and Figure 7).

Table 5: Diagnosis distribution in two groups of patients studied.

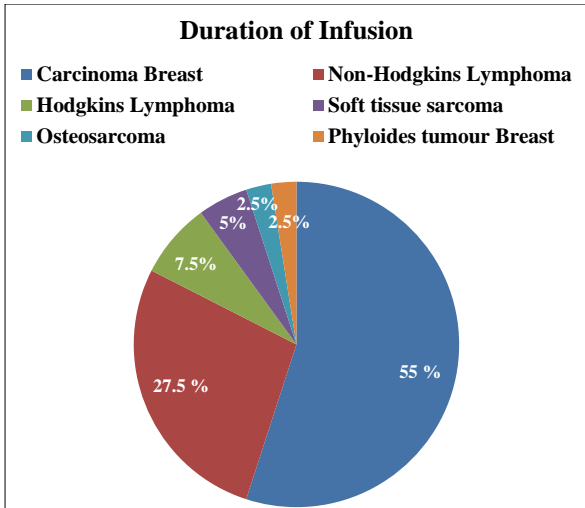| Diagnosis	Duration of Infusion		Total
	15 min	**6 hours**	
Carcinoma Breast	22(55%)	26(65%)	48(60%)
Non-Hodgkins Lymphoma	11(27.5%)	10(25%)	21(26.3%)
Hodgkins Lymphoma	3(7.5%)	2(5%)	5(6.3%)
Soft tissue sarcoma	2(5%)	2(5%)	4(5%)
Osteosarcoma	1(2.5%)	0(0%)	1(1.3%)
Phyloides tumour Breast	1(2.5%)	0(0%)	1(1.3%)
Total	40(100%)	40(100%)	80(100%)
p=0.913, Not Significant, Fisher Exact Test			

Figure 6: Diagnosis distribution in two groups of patients studied.

As shown in (Table 8 and Figure 8), the mean cumulative dose of doxorubicin was 271.5 mg/m^2 in the group which received standard short infusion and 264 mg/m^2 in the group which received the drug by prolonged infusion.

All patients received full course of chemotherapy as planned upfront.

Each patient was clinically assessed (History, Pulse rate and Blood pressure) prior to initiation of chemotherapy, after completion of 200 mg/m^2, 3 months and 6 months after chemotherapy.

Table 6: Chemotherapy regimen distribution in two groups of patients studied.

Chemotherapy regimen	Duration of Infusion		Total
	15 min	6 hours	
AC	22(55%)	26(65%)	48(60%)
R-CHOP	9(22.5%)	6(15%)	15(18.8%)
ABVD	3(7.5%)	2(5%)	5(6.3%)
IA	3(7.5%)	2(5%)	5(6.3%)
CHOP	1(2.5%)	3(7.5%)	4(5%)
CHOP-E	1(2.5%)	1(2.5%)	2(2.5%)
IAP	1(2.5%)	0(0%)	1(1.3%)
Total	40(100%)	40(100%)	80(100%)
p=0.766, Not Significant, Chi-Square Test			

Table 7: Number of cycles and distribution in two groups of patients studied.

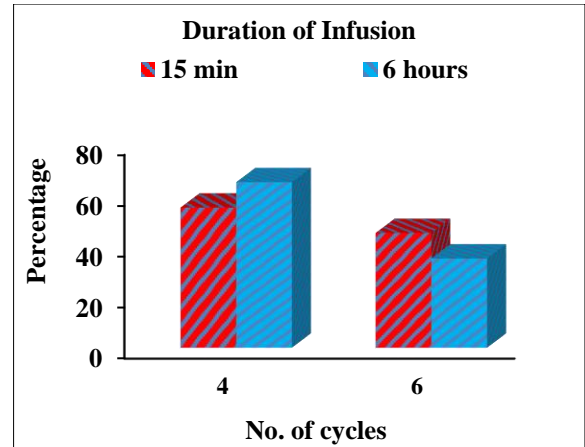| Number of cycles	Duration of Infusion		Total
	15 min	6 hours	
4	22(55%)	26(65%)	48(60%)
6	18(45%)	14(35%)	32(40%)
Total	40(100%)	40(100%)	80(100%)
p=0.361, Not Significant, Chi-Square Test			

Figure 7: Number of cycles and distribution in two groups of patients studied.

Table 8: Dose of Doxorubicin received mg/m^2 and distribution in two groups of patients studied.

Dose of Doxorubicin received mg/m^2	Duration of infusion		Total
	15 min	6 hours	
240	22(55%)	26(65%)	48(60%)
300	15(37.5%)	12(30%)	27(33.8%)
360	3(7.5%)	2(5%)	5(6.3%)
Total	40(100%)	40(100%)	80(100%)
Mean±SD	271.50±38.40	264.00±35.43	267.75±36.90

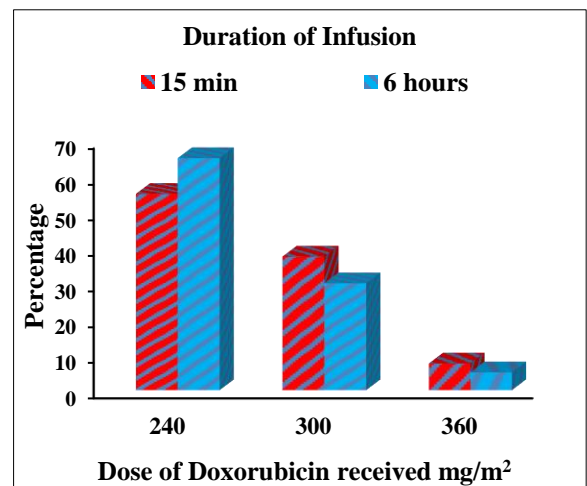**p=0.367, Not Significant, Student t-test**

Figure 8: Dose of Doxorubicin received mg/m^2 and distribution in two groups of patients studied.

None of the patients developed any cardiac symptoms during or after the planned chemotherapy. There was no drop in Left Ventricular Ejection Fraction on serial ECHO during the period of the study. This is depicted in (Table 9).

Table 9: Comparison of ECHO-LVEF in two groups of patients studied.

LVEF	Duration of Infusion		p-value Student t-test
	15 min	6 hours	
ECHO- LVEF-1 (Before chemo)	59.00±2.03	59.13±1.92	0.778
ECHO- LVEF-2 (After completion of >200 mg/m² of Doxorubicin)	59.00±2.03	59.13±1.92	0.778
ECHO-LVEF-3 (3 months after chemo)	59.00±2.03	59.13±1.92	0.778
ECHO-LVEF-4 (6 months after chemo)	59.00±2.03	59.13±1.92	0.778

DISCUSSION

Anthracyclines are among the most commonly used chemotherapy drugs. However, their efficacy is sidelined by potential life-threatening cardiotoxicity. Anthracycline induced cardiotoxicity is potentiated when the cumulative dose of doxorubicin exceeds 300 mg/m². Symptomatic heart failure is rare with cumulative dose of 240 mg/m². However asymptomatic cardiac toxicity is seen even with these cumulative doses as noted. In the North Central Cancer Treatment Group (NCCTG) N9831 trial, after four cycles of anthracycline-containing chemotherapy, 8.5% of 2,992 breast cancer patients had an asymptomatic left-ventricular ejection fraction (LVEF) decline ≥10% but <15% compared with baseline, and 5.0% had an asymptomatic decline >15% or ≤15% to below the lower limit of normal.[2]

Although there is no generally accepted way to limit or prevent anthracycline cardiotoxicity, various strategies have been adopted which includes use of prolonged infusion, the synthesis of analogues of the natural compounds, the development of tumor-specific formulations, and the use of cardioprotective agents.[10]

The rationale for in fusional administration of the chemotherapeutic agents is generally based upon the observations of schedule dependency in experimental systems and drug pharmacology in which a short plasma half-life, following bolus administration, would limit tumor cell exposure. Furthermore, the infusion schedule may reduce the acute and chronic toxic effects commonly associated with high peak levels.[11]

Irrespective of the regimen in which it was included, the 6-hour infusion of doxorubicin was associated with a significantly lower cardiotoxicity than the standard rapid infusion arm. These results were apparent when the physiological parameters of fall in LVEF and decline in QRS voltage were compared as well as when the ultimate end point of congestive heart failure was used for comparison.[5]

There is increased awareness of the cardiotoxicity associated with anthracyclines in the general population. Most of the older studies done earlier to assess Doxorubicin induced cardiotoxicity had cumulative doxorubicin doses of >300 mg/m². But most of the present day doxorubicin containing regimens have doses of anthracyclines between 200 and 300 mg/m², very few regimens go beyond 350 mg/m². We wanted to study the incidence of cardiotoxicity with these newer regimens.

In this study 80 patients who presented to our institute with malignancy and who were planned for Doxorubicin containing chemotherapy regimens >200 mg/m² were included in the study. There were 2 groups (Standard short infusion group or prolonged infusion group) with 40 patients in each group. The patients meeting the inclusion criteria were randomized to either of the groups using the chit method. However, in study conducted by Shapira et al, although 62 consecutively admitted female patients were included the study initially, 4 patients were excluded later making the total study population as 58 patients, 28 in the standard arm and 30 in the 6 hour infusion arm. The allocation to either treatment group was determined according to the last digit of their national identification number: even numbers received the standard method; odd numbers the prolonged infusion.

The mean age of the total study population was 44.34 years with majority if patients being in the age group 41 to 50 years. Standard short infusion group had mean age of 44.60 years while the mean age for the prolonged infusion group was 44.08 years. Patients above the age of 60 years accounted only for 10% of the study population. In comparison the study done by Shapira et al, had mean age of 55 years in the standard infusion group and 53 in the prolonged infusion group. Hence this study had more elderly population compared to our study.

There were total of 57 females and 23 males distributed evenly in the 2 groups. The standard short infusion arm had 27 females and 13 males while the prolonged infusion arm had 30 females and 10 males. Compared to this, the study done by Shapira et al, had only female patients. Majority of the patients in our study had a BSA ranging from 1.4-1.8. This accounted for almost 74% of the total study population. The mean height of the study population was 157.16 cm and the mean weight was 55.91 kg.

Author had 48 patients with carcinoma breast, 21 patients with Non-Hodgkins lymphoma and few patients with Hodgkins Lymphoma, soft tissue sarcoma, osteosarcoma and one patient with Phylloides tumour breast. On the other hand, in the study done by Shapira et al, there were 35 patients were carcinoma breast and 23 patients were carcinoma ovary.

Stage III and Stage IV patients constituted almost 86% of the study population in our study. The study done by Shapira et al included only stage III and Stage IV ovarian cancers and Stage IV carcinoma breast.

The chemotherapy regimens used in our study included AC, R-CHOP, CHOP, CHOP-E, ABVD, IA and IAP. Among these regimens, AC regimen was the most commonly used regimen as majority of study population were cases of Carcinoma breast. Shapira et al, used doxorubicin 50 mg/m^2, 5-fluorouracil (5- FU) 500 mg/m^2, and cyclophosphamide 500 mg/m^2 every 3 weeks for carcinoma breast patients, while the patients with ovarian carcinoma received protocol which included doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m2, and cisplatin 50 mg/m^2 every 3 weeks.

Median number of cycles was 4, with 48 patients receiving 4 cycles of chemotherapy and the rest receiving 6 cycles. In the study done by Shapira et al, the median number of cycles received was 8 (range 4-12).

The mean cumulative dose of doxorubicin was 271.5 mg/m^2 in the group which received standard short infusion and 264 mg/m^2 in the group which received the drug by prolonged infusion, only 5 out of the 80 patients received doses more than 300 mg/m^2. However, in the study done by Shapira et al, the mean cumulative dose of doxorubicin was 410 mg/m^2 (range, 200-550) in the group which received the drug by the standard method, over 15 to 20 minutes and 428 mg/m^2 (range, 250-600) in the group which received the drug by a prolonged infusion.

Among the various parameters studied in the two groups, there was statistically significant difference only for weight and BSA. The two study groups were matched for the rest of the parameters.

The study population of 80 patients, only 11 patients had history of co-morbid conditions which included 6 hypertensive patients, 4 patients with diabetes mellitus and one patient with Congenital Heart disease - Atrial Septal Defect - Post surgical closure. All these patients were on regular medication for these respective illnesses. However, in the study by Shapira et al, patients with concomitant systemic disease were excluded.

None of the patients in our study developed any cardiac symptoms or a drop in the Left Ventricular Ejection Fraction or shortening fraction on serial ECHO during the period of the study. As none of the patients in the study developed cardiotoxicity, correlation between ECG changes and NT-pro-BNP values could not be done. However, in the study done by Shapira et al, 4 patients out of the 58 patients included in the study eventually developed congestive cardiac failure, all of whom received doxorubicin according to the standard short infusion. In all four patients this clinical development was preceded by a significant fall in LVEF of more than 30% of the initial value, after a cumulative doxorubicin

dose of 300 mg/m^2 and a further fall of 10% after subsequent two courses of 50 mg/m^2 each. In all four patients there was also a significant decline of more than 25% in the sum of the QRS voltage in the standard leads. The fall in LVEF was greater than 30% after a cumulative dose of 300 mg/m2 doxorubicin and 35% to 45% after a cumulative dose of 400 mg/m^2.[5]

The probable reason why our study did not have any cardiotoxicity would be that the mean age of our study population was one decade lesser compared to the above mentioned study and mean dose of doxorubicin received by the study group was lesser in our study. Limited follow-up period of 6 months in our study also adds to this.

In a meta-analysis done by Smith and et al, 55 published Randomized Controlled Trials were included, a significantly greater risk of clinical cardiotoxicity was found with bolus than with continuous anthracycline infusions (OR 4.13, 95% confidence interval: 1.75-9.72). They concluded that there is a need to improve cardiac monitoring in oncology trials.[4]

However, one of the studies done by Popov et al, in which they compared an eight-hour infusion of doxorubicin (arm A) with intravenous injection of doxorubicin (arm B) in the EAP regimen with respect to toxicity, objective responses, time to progression (TTP) and survival in 120 patients with advanced gastric cancer. No difference was detected (p=0.28) in the response rate of arm A 20% (CR 3; PR 9; 95% CI:10-30) and B 28% (CR 3; PR 14; 95% CI:17-40). But there was a significant difference in Progressive Disease (p=0.005) between arm A(51%) and arm B(36%). TTP(p=0.01) and survival (p=0.02) analyses detected an advantage for arm B Vs arm A. They concluded that bolus injection of doxorubicin is superior to eight-hour doxorubicin infusion in the EAP regimen in terms of survival, TTP and PD without being significantly more toxic.[11]

A Cochrane review of five randomized controlled trials predominantly involving adult patients concluded that continuous infusion of 6 hours or longer significantly reduced the risk of clinical heart failure (and probably also subclinical cardiac damage) when compared with infusions of 1 hour or less [relative risk (RR) 0.27;95% confidence interval (CI) 0.09-0.81]. There was no evidence that continuous infusion reduced response rate or survival. Continuous infusion appear to be clearly less cardiotoxic.[12]

Qintana et al, evaluated 48 patients for early evidence of cardiotoxicity in patients treated with high-dose doxorubicin given as a continuous infusion. Out of the 48 patients enrolled, no patient developed heart failure symptoms; however, 4 out of the 38(10%) patients with serial left ventricular ejection fraction assessments developed subclinical cardiotoxicity (asymptomatic drop in LVEF ≥10%). Twenty-three patients received all six 72-hour cycles of doxorubicin with a mean cumulative dose of 540 mg/m^2. Among these patients, 4%(n=1) developed subclinical

cardiotoxicity. They concluded that doxorubicin cardiotoxicity can be limited by administering doxorubicin as a continuous infusion, allowing higher cumulative dosing to maximize efficacy.[13]

In this study author did not find any difference between standard short infusion and prolonged infusion of Doxorubicin with respect to the incidence of cardiotoxicity as there was no development of acute and early chronic cardiotoxicity in neither of the two groups during six month follow-up. None of the patients developed any cardiac symptoms during the period of study, nor was there a fall in the ejection fraction on ECHO. There was no significant difference in QRS voltage changes between the two groups. They can safely conclude that when total dose of doxorubicin <300 mg/m^2, probability of patient developing acute or early chronic cardiotoxicity is negligible.

ACKNOWLEDGEMENTS

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