Table 3: Liver function tests of the non-hepatotoxic and hepatotoxic patient groups

Test	Non-hepatotoxic		Hepatotoxic		*P* value	R2
	Mean (SD)	SEM	Mean (SD)	SEM		
SGOT (U/L)	27.29 (5.483)	1.465	47.71 (5.483)	1.484	*P*<0.001***	0.7868
SGPT (U/L)	27.29 (5.483)	1.465	44.39 (8.372)	2.237	*P*<0.001***	0.6710
Direct bilirubin (mg/dL)	0.08929 (0.07509)	0.0200	0.5793 (0.3736)	0.0998	*P*<0.001***	0.6203
Total bilirubin (mg/dL)	0.7157 (0.1867)	0.0498	2.039 (0.6538)	0.1747	*P*<0.001***	0.7796

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, SEM: Standard error mean, ***Highly significant

Age distribution of the study population at this study site has shown that the adult population was mostly affected. A majority of the patients were having rural background, which constitutes about 76.1% (35/46) since this study site is having more rural areas surrounding it and 23.9% (11/46) patients came from urban areas. Among the total patients only 2.7% (1/46) were unmarried, 76.1% (35/46) were married and living with a partner and 21.7% (10/46) were divorced/separated/widowed. As the social status is having a direct relationship with the risk of getting cancers, we collected the information regarding social status of patients with a personal interview. In our study group 13.0% (6/46) were having the habit of alcoholism, 15.2% (7/46) were having the habit of smoking, 23.91% (11/46) were having both alcoholism and smoking, 6.5% (3/46) were having the habit of chewing Pan/Gutka/Tobacco and 41.30% (19/46) were having clean habits. These findings are similar to the past studies in South India.[17]

Of the total population, most of the patients were illiterate, which accounts for 69.6% (32/46), 21.7% (10/46) were having primary educational status, 8.7% (4/46) were having secondary level educational status. Higher educational status was zero in this patient group. These results are showing the poor educational status of this study group. Menopausal status has shown that the 43.5% (20/46) were in pre-menopausal status, 50% (23/46) were having the post-menopausal status and the menopausal status of 6.52% (3/46) patients is unknown because of reasons like unwillingness of patients to reveal. Occupationally 36.95% (17/46) patients were housewives, 21.7% (10/46) were agricultural labors, 6.5% (3/46) were farmers and 34.8% (16/46) were daily wages. As revealed by the patients the reasons for admission include nipple discharge in breast among 84.8% (39/46) patients, lumps in the breast among 15.2% (7/46) patients. These are the main symptoms they had experienced before the exact diagnosis of breast cancer. Body mass index of the patients were calculated during the patient recruitment and found that 36.9% (17/46) were underweight, 56.5% (26/46) were having normal weight and 6.5% (3/46) were having overweight. There were no obese patients in this study group. Since, the prevalence of underweight was more among these patients, there is a great need to provide dietary counseling based on their financial and educational status.[18]

Elevation of liver enzymes and function tests can often be difficult to determine in a patient clinical setting. Our investigation revealed that the incidence of hepatotoxicity associated with Inj. Doxorubicin was 30.4% (14/46) based upon our predefined criteria which were supported by the study of Llesuy and Arnaiz.[19] In a study by Yang *et al*., almost 40% of the patients suffered liver injury after doxorubicin treatment.[20] In order to evaluate hepatotoxicity in the study group, liver function tests such as, SGOT, SGPT, Direct Bilirubin, Total Bilirubin were assessed from pre-chemotherapy to completion of four chemotherapy cycles. Our criteria of utilizing elevation of transaminases and bilirubin have been reported by other investigators prior as a surrogate for liver function during drug therapy.[21] In this study, the mean (SD) of the SGOT in the pre-chemotherapy cycle and fourth chemotherapy cycle were found to be 21.97 (5.798) U/L and 181.3 (103.6) U/L simultaneously which is a significant increase ($P < 0.001$). Mean (SD) of SGPT was found to increased significantly ($P < 0.001$) from 23.17 (6.237) U/L to 147.6 (90.9) U/L. Direct Bilirubin was increased from 0.1351 (0.1186) mg/dL to 0.5445 (0.4587) mg/dL and Total Bilirubin was increased from 0.3094 (1.346) mg/dL to 2.7163 (1.898) mg/dL where $P < 0.04$ and $P < 0.03$ simultaneously, which were statistically significant. After controlling for concurrent hepatotoxic exposures (chemotherapy), there were no correlates (e.g. hemoglobin) for this adverse drug event when utilizing a multivariate logistic regression model.

Prior investigations by Llesuy and Arnaiz have determined that the administration of doxorubicin produced increases of 51% and 53% in liver spontaneous chemiluminescence and malonaldehyde formation respectively.[19] Characteristics of the population were an elevation in serum transaminases and bilirubin. The proposed mechanism for this observation centers on the free radical hypothesis that Doxorubicin undergoes one-electron reduction through nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome P-450 reductase and decreases in antioxidant enzyme, Superoxide dismutase, and catalase activity while the increase in the malondialdehyde levels.[19,22,23] Similarly the mean (SD) values of SGOT, SGPT, direct bilirubin, total bilirubin of patients who have developed hepatotoxicity and patient group who didn't develop hepatotoxicity were compared and found that there exists a highly significant ($P < 0.001$) difference between those two groups with reference to all liver function tests. Based on this study, it appears that Inj. Doxorubicin have the potential to develop hepatotoxicity,

and precautions should be taken including optimizing the dosage pattern, providing appropriate concentration, dosage, and treatment schedule of antioxidants such as vitamin E, vitamin C, vitamin A, antioxidant components of virgin olive oil and selenium as dietary supplements as well as administration as chemotherapeutic agents, by which the anti-tumor action can be maximized and toxicity especially hepatotoxicity of Inj. Doxorubicin can be minimized.[24,25]

Limitations of the Study

The first limitation was that the cohort used to define our patient population for this study was split between the intensive care unit and oncology medicine floor at 24% and 76% respectively. Additional limitations include that the study is single-centered and contains relatively small number of patients. Another limitation of the study was that to truly see the effect of Inj. Doxorubicin on liver, it should be the only exposure to the patient. However, patients that would require Inj. Doxorubicin therapy may be exposed to additional hepatotoxins. The patient population that are receiving chemotherapy often have underlying disease process (i.e., cancer) and/or exposure to risk factors (i.e., medications, intravenous contrast) for the development of hepatotoxicity.

Conclusion

From these results, we can conclude that there exist a strong correlation between the use of Inj. Doxorubicin and risk for developing hepatotoxicity among the breast cancer patients at this study site. These findings are showing that the health-care professionals need to have awareness for hepatotoxicity with the use of Inj. Doxorubicin therapy. A weakness of our analysis is that it may not include the statistical correlations of socio-demographic factors such as age, dose escalation, or cumulative dose. There are multiple reasons for and consequences of hepatotoxicity in this population and there is a need for future interventions to target each specific aspect of hepatotoxicity.

Acknowledgments

We are grateful to Vaagdevi College of Pharmacy/Kakatiya University, Mahatma Gandhi Memorial (MGM) Hospital, St. Ann's Hospital, Warangal, Andhra Pradesh, India and All India Council for Technical Education (AICTE), New Delhi, India.

References

1. Superfin D, Iannucci AA, Davies AM. Commentary: Oncologic drugs in patients with organ dysfunction: A summary. Oncologist 2007;12:1070-83.
2. Henderson IC, Frei E 3rd. Adriamycin cardiotoxicity. Am Heart J 1980;99:671-4.
3. "Doxorubicin (Systemic)." Mayo Clinic. Last updated on: 1999 June 15; Retrieved on 2011 January 26. Archived 2007 April 3 at the Wayback Machine.
4. Fornari FA, Randolph JK, Yalowich JC, Ritke MK, Gewirtz DA. Interference by doxorubicin with DNA unwinding in MCF-7 breast tumor cells. Mol Pharmacol 1994;45:649-56.
5. Momparler RL, Karon M, Siegel SE, Avila F. Effect of adriamycin on DNA, RNA, and protein synthesis in cell-free systems and intact cells. Cancer Res 1976;36:2891-5.
6. Ishak KG, Zimmerman HJ. Morphologic spectrum of drug-induced hepatic disease. Gastroenterol Clin North Am 1995;24:759-86.
7. Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990;11:272-6.
8. Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. Hepatology 1997;26:664-9.
9. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med 2000;342:1266-71.
10. Lee WM. Drug-induced hepatotoxicity. N Engl J Med 1995;333:1118-27.
11. Huet PM, Villeneuve JP, Fenyves D. Drug elimination in chronic liver diseases. J Hepatol 1997;26 Suppl 2:63-72.
12. Schenker S, Martin RR, Hoyumpa AM. Antecedent liver disease and drug toxicity. J Hepatol 1999;31:1098-105.
13. Hardenbergh PH, Recht A, Gollamudi S, Come SE, Hayes DF, Shulman LN, *et al*. Treatment-related toxicity from a randomized trial of the sequencing of doxorubicin and radiation therapy in patients treated for early stage breast cancer. Int J Radiat Oncol Biol Phys 1999;45:69-72.
14. Mohan M, Kamble S, Satyanarayana J, Nageshwar M, Reddy N. Protective effect of *Solanum torvum* on Doxorubicin-induced hepatotoxicity in rats. Int J Drug Dev Res 2011;3:131-8.
15. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med 2006;354:731-9.
16. Damodar G, Smitha T, Gopinath S, Vijayakumar S, Rao YA. Assessment of quality of life in breast cancer patients at a tertiary care hospital. Arch Pharma Pract 2013;4:15-20.
17. Damodar G, Smitha T, Rao YA. A descriptive epidemiological study of cancers at a South Indian tertiary care hospital. Res J Pharm Biol Chem Sci 2011;2:907-15.
18. Damodar G, Vijayakumar S. Implementation of dietary counselling for low socioeconomic cancer patients: A review. Int J Comm Pharm 2011;4:5-13.
19. Llesuy SF, Arnaiz SL. Hepatotoxicity of mitoxantrone and doxorubicin. Toxicology 1990;63:187-98.
20. Yang XL, Fan CH, Zhu HS. Photo-induced cytotoxicity of malonic acid C (60) fullerene derivatives and its mechanism. Toxicol *in vitro* 2002;16:41-6.
21. Floyd J, Mirza I, Sachs B, Perry MC. Hepatotoxicity of chemotherapy. Semin Oncol 2006;33:50-67.
22. Lee V, Randhawa AK, Singal PK. Adriamycin-induced myocardial dysfunction *in vitro* is mediated by free radicals. Am J Physiol 1991;261:H989-95.
23. Kalender Y, Yel M, Kalender S. Doxorubicin hepatotoxicity and hepatic free radical metabolism in rats. The effects of vitamin E and catechin. Toxicology 2005;209:39-45.

24. Chen Y, Jungsuwadee P, Vore M, Butterfield DA, St Clair DK. Collateral damage in cancer chemotherapy: Oxidative stress in nontargeted tissues. Mol Interv 2007;7:147-56.
25. Granados-Principal S, Quiles JL, Ramirez-Tortosa CL, Sanchez-Rovira P, Ramirez-Tortosa MC. New advances in molecular mechanisms and the prevention of adriamycin toxicity by antioxidant nutrients. Food Chem Toxicol 2010;48:1425-38.

How to cite this article: Damodar G, Smitha T, Gopinath S, Vijayakumar S, Rao YA. An evaluation of hepatotoxicity in breast cancer patients receiving injection doxorubicin. Ann Med Health Sci Res 2014;4:74-9.

Source of Support: Vaagdevi College of Pharmacy/Kakatiya University, Warangal, Andhra Pradesh and All India Council for Technical Education (AICTE), New Delhi, India. **Conflict of Interest:** None declared.