Original Article

DOI: 10.29054/APMC/19.691

Simulation Models for Comparison of Toxicities of Anticancer Drugs

Muhammad Adeel, Muhammad Khalid, Muhammad Asif, Muhammad Naeem Faisal

ABSTRACT

Objective: This retrospective cohort study presents simulation models for analyzing toxicities of doxorubicin and docetaxel, both in combination of cyclophosphamide (AC and TC). It compared their side effects during postoperative chemotherapy of the treated Pakistani breast cancer patients. **Study Design:** It was retrospective study. **Settings:** Radiotherapy and Oncology Department, Allied Hospital, Faisalabad, Pakistan. **Duration:** Between September 2015 and September 2017. **Methodology:** 188 Patients out of 356 received TC (600 mg/m^2 of cyclophosphamide, 75 mg/m^2 of docetaxel) and 168 received AC (600 mg/m^2 of cyclophosphamide,60 mg/m^2 of doxorubicin). Using simulation and modeling the study presents two simulation models called *SMG$_1$SE*, (Simulation Model for Side Effects listed in Group 1) and *SMG$_2$SE* (Simulation Model for Side Effects listed in Group 2). *SMG$_1$SE* shows drugs toxicity based on side effects, listed in group 1 including muscles pain, mild anemia, moderate anemia, blood transfusion, weight loss, and hands burning. *SMG$_2$SE* shows toxicity based on side effects, listed in group 2 including vomiting, change in taste, sores in throat, diarrhea, tiredness, and dizziness. **Results:** At α=0.05, chi-squared test was used for statistical analysis. No significant difference was observed between the percentages of patients with extreme tiredness, stability, mild anemia, vomiting, and diarrhea for *P*-value remained>0.05. Though, AC(*P*-value<0.05)was found less toxic by 25.7%, 22.6%, 25.3%,20.8%,16.4%, and 12.4% and compared to TC for muscle pain, changes in taste, burning hands, moderate anemia, needing blood transfusion, and change in hemoglobin level, respectively, but TC was found less toxic by 32.5%, 26.3%, and 52.9% for weight loss, sores in throat and mouth, and dizziness respectively. **Conclusion:** At 24 months, AC remained less toxic than TC.

Keywords: Simulation modeling, Quality of life during chemotherapy, Comparison of AC and TC, Clinical markers, Toxicity of anticancer drugs.

Corresponding Author

DR. MUHAMMAD ASIF, Associate Professor, Department of Computer Science, National Textile University, Faisalabad-Pakistan
Contact / Email: +92 333-6444457, asif@ntu.edu.pk

Submitted for Publication: 18-06-2019 *Accepted for Publication: 06-08-2019*

Citation: Adeel M, Khalid M, Asif M, Faisal MN. Simulation Models for Comparison of Toxicities of Anticancer Drugs. APMC 2019;13(3):216-22.

INTRODUCTION

It becomes very hard for the cancer patients to bear the side effects during the chemotherapy. They have to face very poor quality of their life due to the toxicities of anticancer drugs.[1] Even in chemotherapy using platinum-based chemotherapy drugs, patients can experience up to 40 different side effects.[2]

A study reported chemotherapy severe side effects including intracranial hemorrhage, severe hematotoxicity, injection site reaction requiring surgical intervention, and thromboembolism.[3] Sometime patients' treatment also discontinues due to adverse side effect of chemotherapy.[4]

The majority of anticancer drugs, along with tumorous cells, also affect normal cells of the patients and hence they remain very tense thought out the chemotherapy.[5] Cancer patients with grade 1 to grade 4face different types of side effects with different intensity.[6]

There are also, for women with early breast cancer, long term side effects of postoperative chemotherapy.[7] During the most upsetting side effects, cancer patients even die due to chemotherapy cardiac computed tomography-induced heart failure.[8]

Agent based simulation modelling is a programming environment in which a social complex problem is addressed with the involvement of the agents related to that problem under certain rules for their interaction.[9] We aim to presents simulation models for analyzing toxicities anticancer of drugs including doxorubicin plus cyclophosphamide and docetaxel plus cyclophosphamide.

With respect to Medline Plus, NIH US database, there are different side effects of doxorubicin including vomiting, nausea, loss of appetite (and weight loss), sores in the mouth and throat, stomach pain, weight gain, increased thirst, diarrhea, separation of toenail or fingernail, hair loss, tiredness, dizziness, watery, red, or irritated eyes, eye pain, burning, pain, or tingling in hands or feet, red discoloration of urine, skin rash, hives, itching, difficulty in swallowing or breathing, and seizures.[10-12]

METHODOLOGY

Study Design: It was a retrospective cohort study.

Settings: Radiotherapy and Oncology Department, Allied Hospital, Faisalabad, Pakistan

Duration: Between September 2015 and September 2017

Sample Technique: Targeted Population

Sample Size: 356

Inclusion Criteria: Non-diabetic women with age of 28 and 62 years with invasive ductal carcinoma of breast were included in this study.

Exclusion Criteria: Diabetic breast cancer patients of less than 28 or above 62 years with stage IV disease were excluded in this study.

Methods: This retrospective study was composed of two simulation models including *SMG$_1$SE* and *SMG$_2$SE* which were

based on the comparative study of postoperative chemo cycles for toxicities of TC abd AC in female breast cancer.

The data for this study was retrieved during an parroved project, "Genomic study of mutatd gene targeting for identification of sigbling cascade in Breat cancer", with aprroval # 675/2016 by Ethical Review Committee, Punjab Medical College, Faisalabad.

Between September 2015 and September 2017, 188 patients out of 356 received TC (600 mg/m^2 of cyclophosphamide, 75 mg/m^2 of docetaxel) and 168received AC (600 mg/m^2 of cyclophosphamide, 60 mg/m^2 of doxorubicin).

For the inclusion criteria in this study gender-wise, only female patients with age: ≥ 28 and ≤ 62 years with histologically invasive ductal carcinoma were included.

Their ECOG was 0 – 1, of all grades with stage I – III and they had no diabetes with normal FT and the value of their EF in echocardiography was 55% to 70%. Whereas for exclusion criteria, male patients were not included in this study. All patents were excluded with age ≤ 28 and ≥ 62 years and histologically other than invasive ductal carcinoma with ECOG 2 and above. Patients with stage IV (metastasis) with diabetes and abnormal RFT as well as who had their EF value below 50% in echocardiography were also excluded from this study.

Based on clinical markers, the drugs side effects (toxicities because of doxorubicin, docetaxel, and cyclophosphamide) were recorded in this study. Side effects from the records of this study with respect to the listed side effects from the database of NIH US (MedlinePlus) were then filtered to be included to compare in this study.

Net Logo 5.1[13] (Java based simulation software tool for the solution of complex problems) was used with agent-based computer simulation and modeling technique for the development of three simulation models called SMG1SE, (Simulation Model for Side Effects listed in Group 1), SMG2SE (Simulation Model for Side Effects listed in Group 2), and SMTCAL (Simulation Model for Tumor Cells Aggression Level). SMG1SE was developed to show drugs toxicity and efficacy on the basis of side effects, listed in group 1 including muscles pain, mild anemia, moderate anemia, blood transfusion, weight loss, and hands burning.

SMG2SE was developed to show drugs toxicity and efficacy on the basis of side effects, listed in group 2 including vomiting, change in taste, sores in throat, diarrhea, tiredness, and dizziness. SMG1SE and SMG2SE show the interaction of the agents including patients, AC and TC drugs. In both models, the side effects, because of these drugs, are the properties of the showed patients.

The potency, dosage (drugs administration), affecting, and death (drugs elements vanish after affecting) are the properties of the drugs which affect the number of patients of the different showed side effects. Figure 1 and Figure 2 show these agents with their properties.

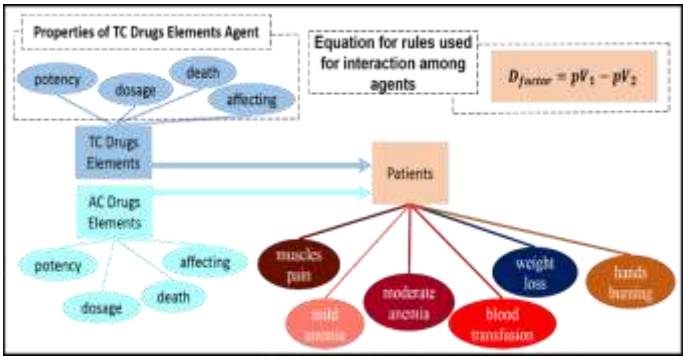


Figure 1: SMG1SE as a complex system with agents and their properties for adaptive behavior in an autonomous environment, with equations for rules used for interaction among agents

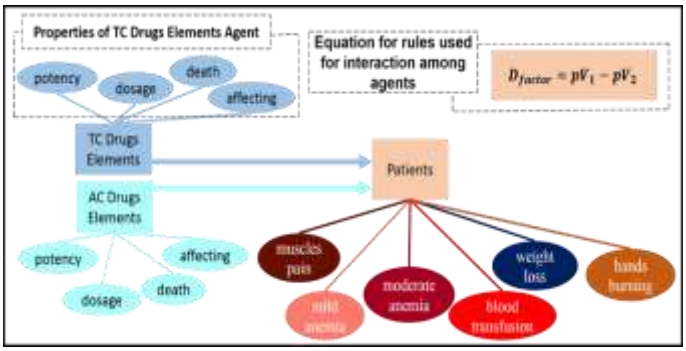


Figure 2: SMG2SE as a complex system with agents and their properties for adaptive behavior in an autonomous environment, with equations for rules used for interaction among agents

There are two controls in the interface of SMG$_1$SE including setup and inject-drugs. The setup control divides the window into two parts for showing patients with mentioned side effects by TC and AC drugs. The inject-drugs control runs the simulation to show the effect of drugs and the status of patients regarding side effects after receiving treatment with TC and AC drugs.

Similarly, there are two simulation controls in the interface of SMG2SE including setup and inject-drugs. The setup control divides the window into two parts for showing patients with mentioned side effects by TC and AC drugs. The inject-drugs control runs the simulation to show the effect of drugs and the status of patients regarding side effects after receiving treatment with TC and AC drugs.

RESULTS

We provided the input of required data in our *SMG$_1$SE* and executed it to see the visual exploration of the developed simulation model. The next sections explain the simulations with results in details.

The execution of *SMG$_1$SE* shows the number of patients affected with different diseases and it also shows the comparison of common factors in both cohorts of patients received chemotherapy using TC and AC drugs. The execution results of *SMG$_1$SE* are shown by Figure 3and Figure 4.

The execution of SMG2SE shows the number of patients affected with different diseases and it also shows the comparison of common factors in both cohorts of patients received chemotherapy TC and AC drugs. The execution results of SMG2SE are shown from Figure 5 to Figure 6.

From the statistical results of SMG_1SE and SMG_2SE (Table 1), it was observed no significant difference between the percentages of patients with extreme tiredness, stability, mild anemia, vomiting, and diarrhea for P-value remained >0.05. Though, AC (P-value <0.05) was found less toxic by 25.7%, 22.6%, 25.3%, 20.8%, 16.4%, and 12.4% and compared to TC for muscle pain, changes in taste, burning hands, moderate anemia, needing blood transfusion, and change in hemoglobin level, respectively, whereas TC was found less toxic by 32.5%, 26.3%, and 52.9% for weight loss, sores in throat and mouth, and dizziness respectively.

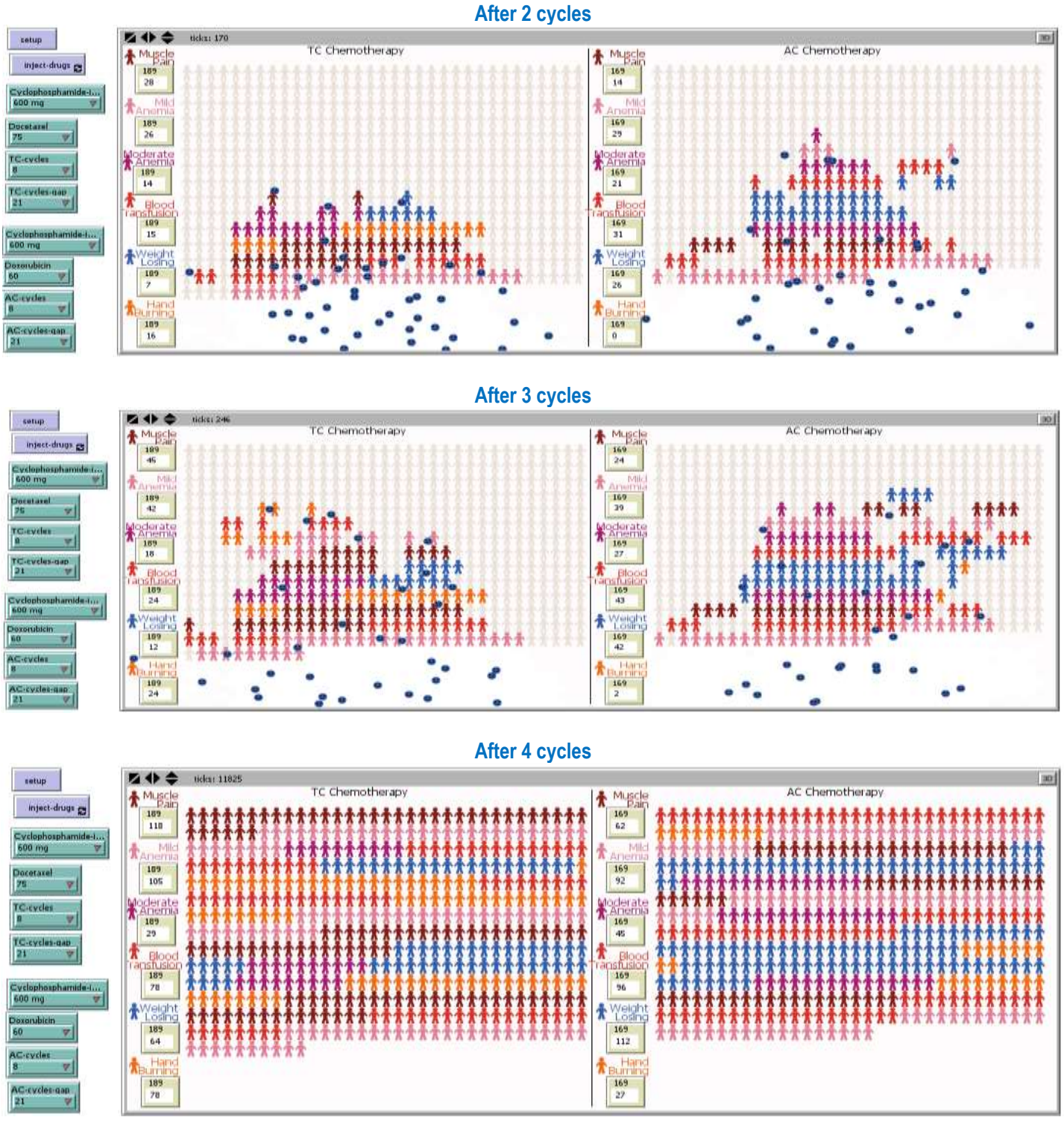


Figure 3: The number of patients with Group 1 side effects, affected by TC and AC drugs

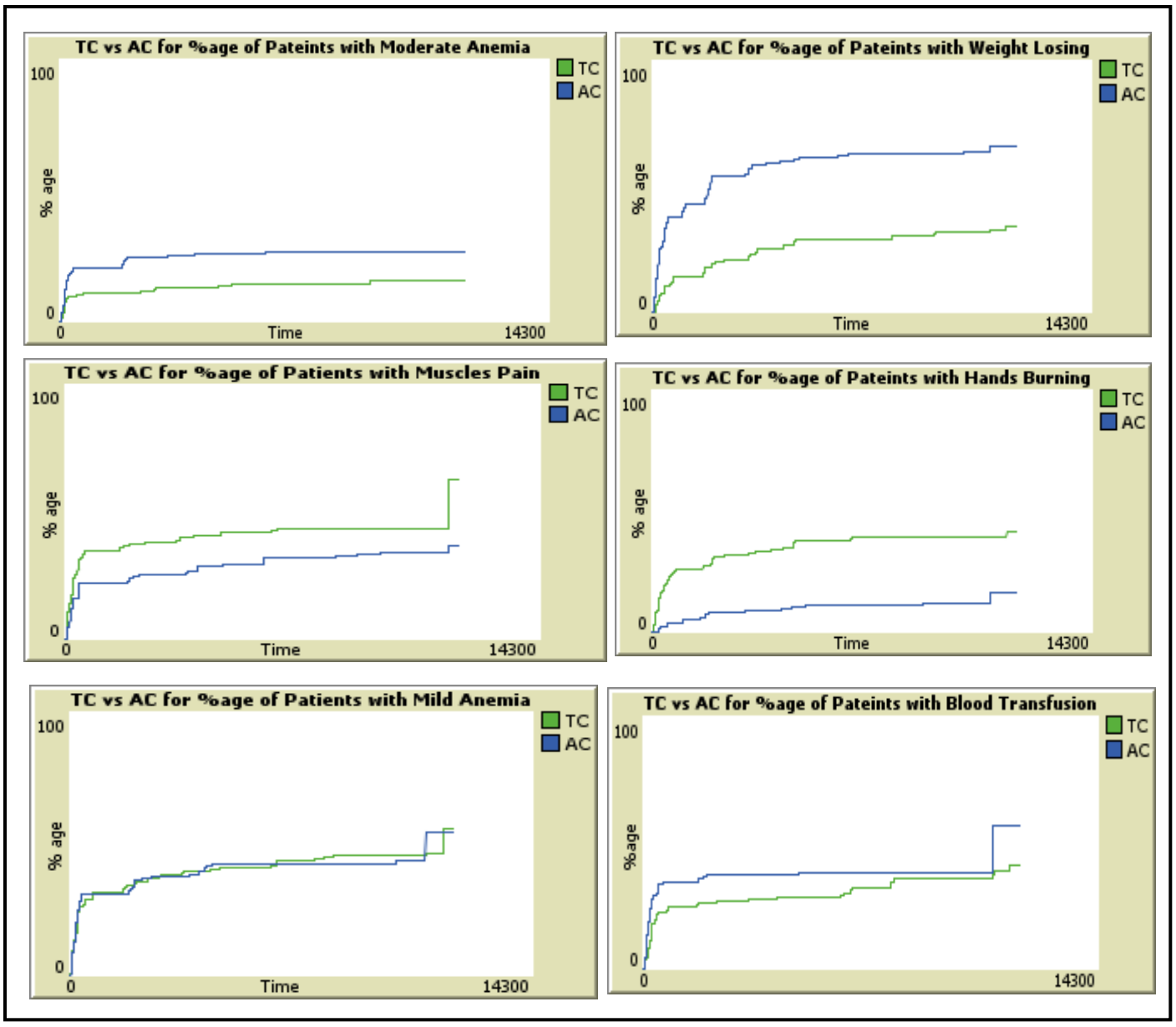
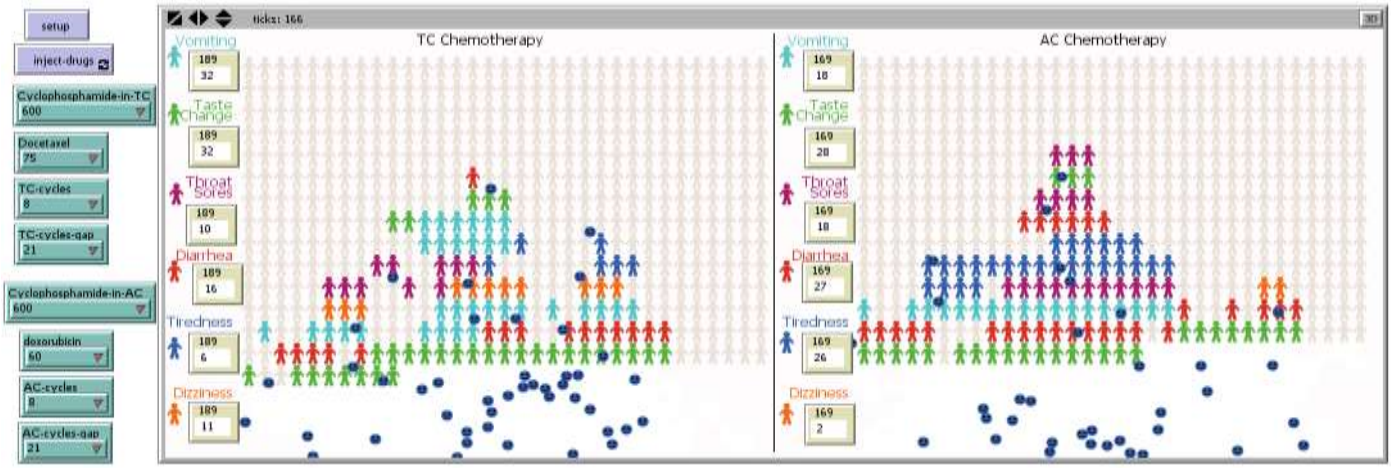
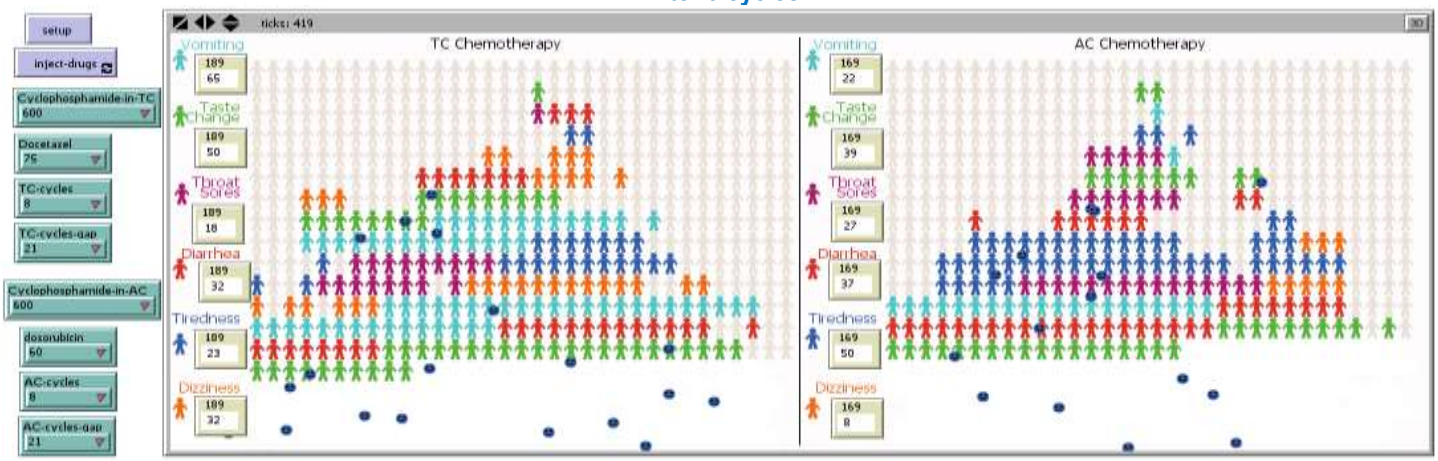


Figure 4: TC and AC for a percentage of patients with the Side Effects of Group 1 after 4 cycles

After 2 cycles



After 3 cycles



After 4 cycles

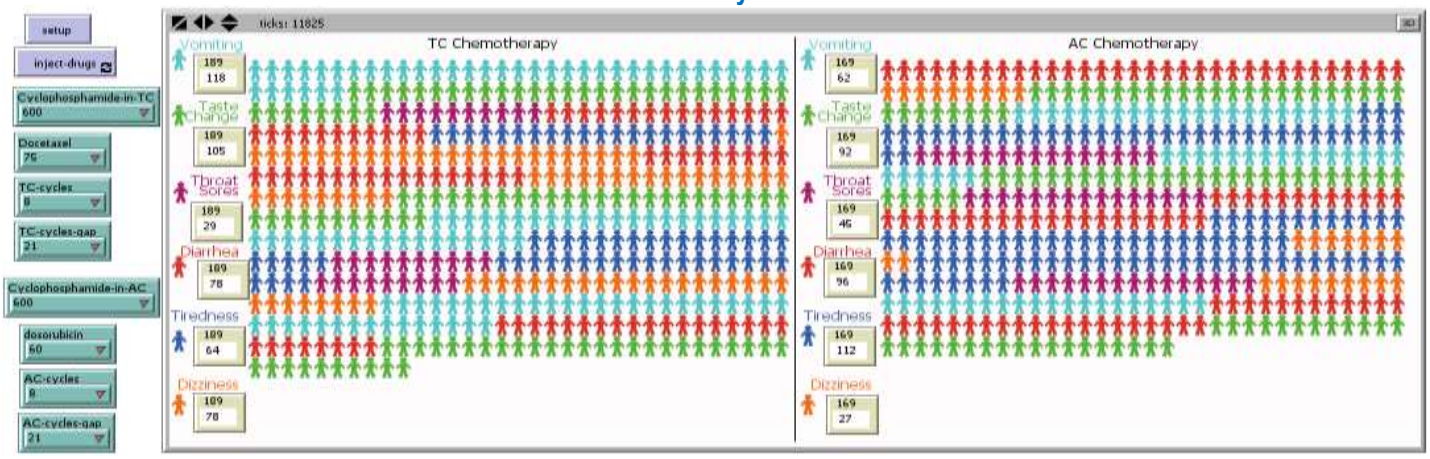


Figure 5: The number of patients with Group 2 side effects, affected by TC and AC drugs

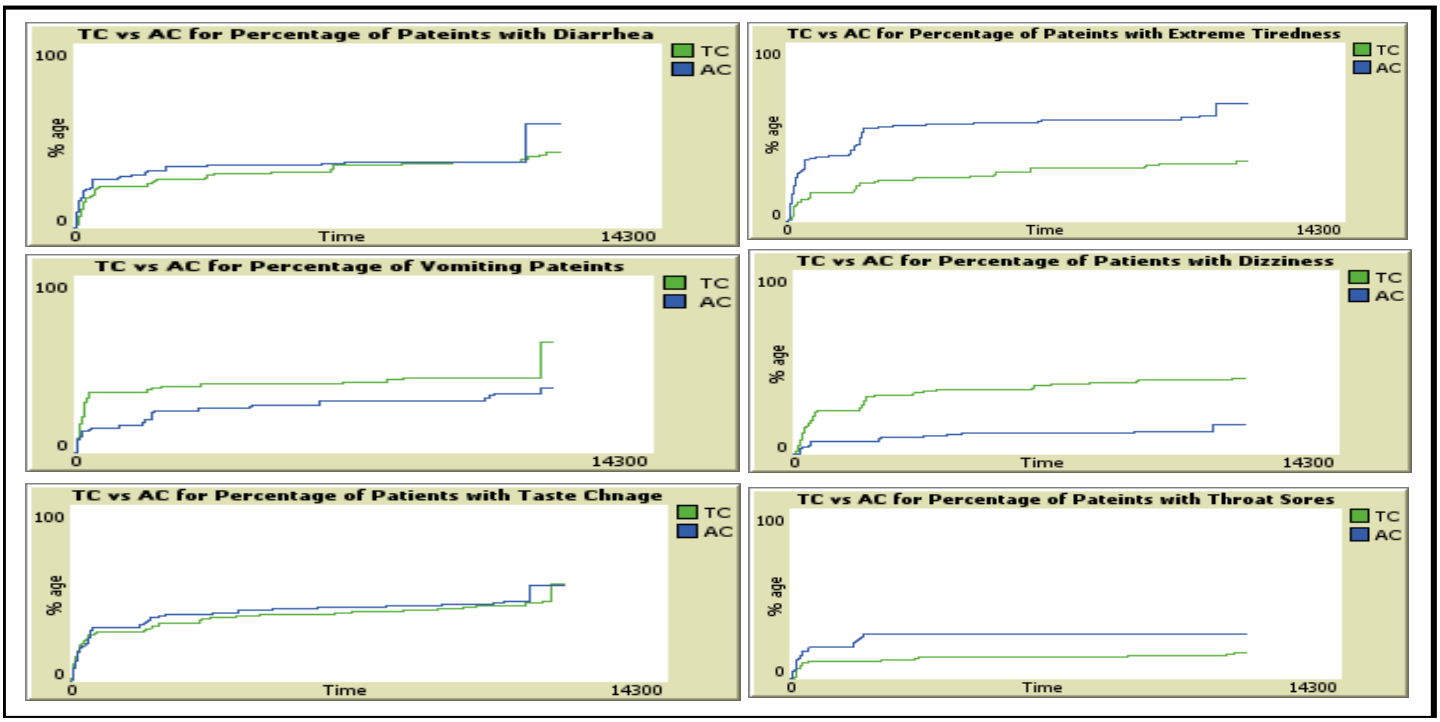


Figure 6: TC and AC for a percentage of patients with the Side Effects of Group 2 after 4 cycles

Table 1: Comparative Analysis of doxorubicin and docetaxel, both in combination of cyclophosphamide

Parameter	Name		Attribute	Docetaxel plus cyclophosphamide		Docetaxel plus cyclophosphamide		Chi-Square Test: α=0.05			
				Number	%	Number	%	X^2	D.F	Critical Value	P-Value
Side Effects	Stability		Stable	66	34.9	57	33.7	0.056	1	3.841	0.812
			Weak	123	65.1	112	66.3				
	Weight	Loss	Yes	64	33.8	112	66.3	38.878	1	3.841	0.000
			No	123	66.1	54	32				
		Gain		2	1.1	3	1.7	-	-	-	-
	Blood Transfusion		Yes	59	31.2	25	14.8	13.402	1	3.841	0.000
			No	130	68.8	144	85.2				
	Vomiting		Yes	177	93.3	149	88.2	3.298	1	3.841	0.069
			No	12	6.3	20	11.8				
	Extreme Tiredness		Yes	168	88.9	153	90.5	0.26	1	3.841	0.61
			No	21	11.1	16	9.5				
	Changes in Taste		Yes	55	29.1	11	6.5	30.283	1	3.841	0.000
			No	134	70.9	158	93.5				
	Muscle Pain		Yes	118	62.4	62	36.7	23.66	1	3.841	0.000
			No	71	37.6	107	63.3				
	Diarrhoea		Yes	19	10.1	22	13	0.773	1	3.841	0.379
			No	170	89.9	147	87				
	Sores in Throat and Mouth		Yes	127	67.2	158	93.5	38.003	1	3.841	0.000
			No	62	32.8	11	6.5				
	Burning in Hands and Feet		Yes	78	41.3	27	16	27.538	1	3.841	0.000
			No	111	58.7	142	84				
	Hair Loss		Yes	189	100	169	100	-	-	-	-
			No	0	0	0	0				
	Dizziness		Yes	51	27	135	79.9	100.014	1	3.841	0.000
			No	138	73	34	20.1				
	Change of Nail Color		Yes	189	100	169	100	-	-	-	-
			No	0	0	0	0				
	Mild Anemia		Yes	105	55.6	92	54.4	0.045	1	3.841	0.832
			No	84	44.4	77	45.6				
	Moderate Anemia		Yes	75	39.7	32	18.9	18.328	1	3.841	0.000
			No	114	60.3	137	81.1				

DISCUSSION

There are a number of studies presented for disease related quality of life (health status) and toxicity of chemotherapy for breast cancer women.[14-16] There are different chemotherapy combinations as adjuvant chemo in breast cancer,[17] especially, as the first line, combinations of doxorubicin with docetaxel and cyclophosphamide with doxorubicin of chemo in aggressive disease.[18] From the physical assessment of the patients in this study, it was derived that the quality of life of around 70% patients remained very poor.

It was noted that the most of these patients were from rural areas with low economical families, this is why with poor diet and inappropriate (not neat and clean) environment, they were leading a very hard life as compare to the rest 30% patients who received good diet and neat and clean atmosphere.

The major cause of toxicities of anticancer drugs is the affected normal cells that are disturbed by these drugs along with tumors cells.

Targeted therapy may reduce this factor at some extent but not completely as it should be for leading a normal life for cancer patients during and after treatment. Health care centers are playing a very good role in this regard but these centers only care the patients look and feel. Disturbance of the normal cells, due to anticancer drugs, cannot be stopped.

CONCLUSION

It is concluded that at 24 months, AC remained less toxic than TC.

LIMITATIONS OF THE STUDY

However, some limitation should be noted for this study. We could not get some follow up reports for the side effects status after the patients left the hospital.

SUGGESTIONS

The sample size should be improved for better results.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

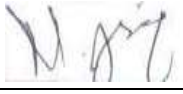
ACKNOWLEDGEMENT

We acknowledge the facilitation in data collection provided by staff of Radiotherapy and Oncology department of Allied Hospital, Faisalabad Pakistan.

REFERENCES

1. Carlson LE, Subnis UB, Piedalue KAL, Vallerand J, Speca M, Lupichuk S, et al. The ONE-MIND Study: Rationale and protocol for assessing the effects of ONlinE MINDfulness-based cancer recovery for the prevention of fatigue and other common side effects during chemotherapy. European journal of cancer care. 2019:e13074.
2. Oun R, Moussa YE, Wheate NJ. The side effects of platinum-based chemotherapy drugs: a review for chemists. Dalton Trans. 2018;47(19):6645-53.
3. Jungk C, Chatziaslanidou D, Ahmadi R, Capper D, Bermejo JL, Exner J, et al. Chemotherapy with BCNU in recurrent glioma: Analysis of clinical outcome and side effects in chemotherapy-naïve patients. BMC cancer. 2016;16(1):81.
4. Demaria M, O'Leary MN, Chang J, Shao L, Liu S, Alimirah F, et al. Cellular senescence promotes adverse effects of chemotherapy and cancer relapse. Cancer Discov. 2017;7(2):165-76.
5. Krukiewicz K, Zak JK. Biomaterial-based regional chemotherapy: local anticancer drug delivery to enhance chemotherapy and minimize its side-effects. Mater Sci Eng C Mater Biol Appl. 2016;62:927-42.
6. Pearce A, Haas M, Viney R, Pearson S-A, Haywood P, Brown C, et al. Incidence and severity of self-reported chemotherapy side effects in routine care: a prospective cohort study. PLoS One. 2017;12(10):e0184360.
7. Tao JJ, Visvanathan K, Wolff AC. Long term side effects of adjuvant chemotherapy in patients with early breast cancer. Breast. 2015;24(2):149-53.
8. Norwood Toro LE, Hader SN, Kong A, Rui H, Beyer AM. Adverse Effects of Chemotherapy on Human Microvascular Function. The FASEB J. 2019;33(1):453-63.
9. Macal CM. Everything you need to know about agent-based modelling and simulation. J Simulation. 2016;10(2):144-56.
10. Medline Plus. Side Effects of Doxorubicin: NIH US National Library 2019 Available from: https://medlineplus.gov/druginfo/meds/a682221.html.
11. MedlinePlus. Side Effects of Docetaxel NIH US National Library 2019 [updated 17 June 20192 July 2019]. Available from: https://medlineplus.gov/druginfo/meds/a696031.html.
12. MedlinePlus. Side Effects of Cyclophosphamide: NIH US National Library [updated 17 June 20192 July 2019]. Available from: https://medlineplus.gov/druginfo/meds/a611044.html.
13. Wilensky U. NetLogo 1999-2105 [April 26, 2105]. Available from: http://ccl.northwestern.edu/netlogo/.
14. Martin M, Lluch A, Segui M, Ruiz A, Ramos M, Adrover E, et al. Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC): impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen. Annals of oncology. 2006;17(8):1205-12.
15. Hoffmann T, Corrêa-Fissmer M, Duarte CS, Nazário RF, Barranco ABS, Oliveira KWKd. Prevalence of dermatological complaints in patients undergoing treatment for breast cancer. An Bras Dermatol. 2018; 93(3): 362–7.
16. Bayo J, Aviñó V, Toscano F, Jiménez F. Toxicity of docetaxel, carboplatin, and trastuzumab combination as adjuvant or neo-adjuvant treatment for Her2 positive breast cancer patients and impact of colony-stimulating factor prophylaxis. Breast J. 2018;24(4):462-467.
17. Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnatelli L, Brambilla C, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med. 1976;294(8):405-10.
18. Jones SE, Savin MA, Holmes FA, O'shaughnessy JA, Blum JL, Vukelja S, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol. 2006;24(34):5381-7.

AUTHORSHIP AND CONTRIBUTION DECLARATION

AUTHORS	Contribution to The Paper	Signatures
Muhammad Adeel Department of Computer Science, National Textile University, Faisalabad, Punjab, Pakistan	Data Collection, Study Designing, Analysis of Data and paper writing with Final Approval	
Dr. Muhammad Khalid Associate Professor, Clinical Oncology Department, Faisalabad Medical University, Allied Hospital, Faisalabad, Pakistan	Analysis of Data, Study Designing and paper writing with Final Approval	
Muhammad Asif Department of Computer Science, National Textile University, Faisalabad, Punjab, Pakistan	Analysis of Data and paper writing with Final Approval	
Dr. Muhammad Naeem Faisal Faculty of Veterinary Science, Institute of Pharmacy, Physiology, and Pharmacology, University of Agriculture, Faisalabad, Pakistan	Analysis of Data and paper writing with Final Approval