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/m² of cyclophosphamide, 75 mg/m² of docetaxel) and 168 received AC (600 mg/m² of cyclophosphamide, 60 mg/m² of doxorubicin). Using simulation and modeling the study presents two simulation models called SMG;SE, (Simulation Model for Side Effects listed in Group 1) and SMG;SE (Simulation Model for Side Effects listed in Group 2). SMG;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;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 weight, 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.

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. Even in chemotherapy using platinum-based chemotherapy drugs, patients can experience up to 40 different side effects. A study reported chemotherapy severe side effects including intracranial hemorrhage, severe hematotoxicity, injection site reaction requiring surgical intervention, and thromboembolism. Sometime patients’ treatment also discontinues due to adverse side effect of chemotherapy. 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. Cancer patients with grade 1 to grade 4 face different types of side effects with different intensity. There are also, for women with early breast cancer, long term side effects of postoperative chemotherapy. During the most upsetting side effects, cancer patients even die due to chemotherapy cardiac computed tomography-induced heart failure. 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. 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.

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 and above 62 years with stage IV disease were excluded in this study. Methods: This retrospective study was composed of two simulation models including SMG;SE and SMG;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 approved project, “Genomic study of mutatd gene targeting for identification of sigbling cascade in Breast cancer”, with approval # 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/m² of cyclophosphamide, 75 mg/m² of docetaxel) and 168 received AC (600 mg/m² of cyclophosphamide, 60 mg/m² 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 patients 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.

NetLogo 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 STMCAL (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.

RESULTS

We provided the input of required data in our SMG1SE 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 SMG1SE 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 SMG1SE are shown by Figure 3 and 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$_1$SE and SMG$_2$SE (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

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 Group 2 side effects after 4 cycles

Figure 6: TC and AC for a percentage of patients with the Side Effects of Group 2 after 4 cycles
DISCUSSION
There are a number of studies presented for disease related quality of life (health status) and toxicity of chemotherapy for breast cancer women. There are different chemotherapy combinations as adjuvant chemo in breast cancer, especially, as the first line, combinations of doxorubicin with docetaxel and cyclophosphamide with doxorubicin of chemo in aggressive disease. 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.
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REFERENCES

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