RESEARCH ARTICLE

Computer Simulation Modeling for Analyzing Mammary Gland Tumor Cells Aggression Level Restricted by Comparative Chemotherapy using Docetaxel and Doxorubicin Both with Cyclophosphamide

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A B S T R A C T

Using simulation modeling, this study analyzes "tumor cells aggression level" (TCAL) in mammary gland tumor-induced rat models by chemotherapy with docetaxel plus cyclophosphamide (TC) and doxorubicin plus cyclophosphamide (AC). The presented "simulation model for TC and AC" (SMTA) compares the efficacy of these drugs against TCAL by providing visual interaction of the drugs with tumor cells. It will help to decide the better drug combination for controlling TCAL. Mammary gland tumor was induced in 389 rat models using 2.5 mg N-methyl-N-nitrosourea in 0.2 mL normal saline. For four chemo cycles, 198 rats were treated with TC and 191 with AC. Using published and derived equations, rules were programmed for observing interactions among SMTA agents. Two-sample t-test, at $\alpha=0.05$, was applied for statistical analysis of rat model results. For validation, paired t-test was used to compare SMTA, rat models, and published results. Analyzing rat models, there was a significant statistical difference between overall change in Hb level and WBC count affected by TC and AC. P-value=0.000<0.05, for both Hb level and WBC count, affected 3.98% and 5.13% respectively more by TC than AC. Providing SMTA with same drugs administration, given to rat models, 3.8% more tumor cells were controlled by AC than TC. Validating results from rat models and SMTA, there was no significant difference between means of overall trend in change of: (i) Hb level (p-value= 0.795>0.05), (ii) WBC count (p-value= 0.374>0.05). AC remained better than TC in controlling TCAL with a lesser effect on WBC count and Hb level.

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INTRODUCTION

Agent-based modeling and simulation is the process of simulating the solution of complex problems by making a model of different domains (Macal, 2016). In this process, the interactions of the agents involved in the system show their influence on one another in an environment with multifaceted and different situations which vary with the passage of time (Fredrich *et al.,* 2018). Agents are components that have adaptive behavior in an autonomous environment under certain varying situations for the solution of a complex problem (Macal, 2016). Cancer treatment is one of the best examples of complex systems for which "agent-based modeling and simulation" has been widely applied (Wang *et al.,* 2015).

Tumor of mammary gland is one of the most fatal diseases (Miller *et al.,* 2016*)* which may be invasive or non-invasive in nature, usually caused by the developmental abnormalities in mammary gland cells (Gradishar *et al.,* 2017*)*. According to a report of the American Cancer Society, 522,000 females died due to breast cancer in 2018 (Ferlay *et al.,* 2019).

Tumor cells aggression level means how quickly tumor cells proliferate, metastasize with the involvement of lymphatic system (Adams *et al.,* 2016). Change in the rate of cellular proliferation or apoptosis is the key to get decrement or increment of TCAL (Adams *et al.,* 2016). The cell circulatory system of the patients also plays a vital role in the increment or decrement of TCAL (Smerage *et al.,* 2014). In early-stage of breast cancer,

chemotherapy is started in different ways by oncologists to control the aggression level (Zhao *et al.*, 2019) through mitotic and metabolic inhibitors. These inhibitors control the metabolic activities that supply nutrition to tumor cells resulting in an arrest of mitotic division of the cells (Senkus *et al.*, 2015). Through TCAL, the efficacy of anti-cancer drugs can be measured by clinical trials followed by assessment tests (Senkus *et al.*, 2015). Cancer is also graded by TCAL for defining its possible stages (Giuliano *et al.*, 2017). In cancer patients, the ineffectiveness of chemotherapy results in higher value of TCAL and lowering of WBC count (Fan *et al.*, 2016). Therefore, there is an intense need for measuring TCAL to evaluate the efficacy of chemotherapy. Chemotherapy of cancer patients also results in lowering of Hb level (Parker *et al.*, 2018) which causes improper drug delivery to tumor cells. If the concentration of chemotherapy is decreased at the cellular level, then the tumorous cells' proliferation becomes more aggressive. Therefore, there is also an intense need of drugs administration at an appropriate level. The relation among TCAL, drugs administration, WBC count, and Hb level becomes a very complex problem of this complicated system in cancer treatment assessment. Since cancer treatment involves risk of life, therefore it is difficult to do real experiments on patients, moreover, in case of animals, real experiments require a considerable time and resources (Saluja *et al.*, 2018) to evaluate the efficacy and toxicity of anticancer drugs. Such complex problems can be effectively solved using agent-based modeling and simulation technique utilizing considerably minimum time, energy and resources (Macal, 2016).

Literature shows a massive work in the field of anticancer research including TC and AC and results are being used for clinical trials and practices. This work can be further enhanced and facilitated using computational simulation techniques (Wang *et al.*, 2015). Previously two approaches, agent-based modeling and pharmacokinetic-pharmacodynamic modeling have been discussed for integrating them in oncology (Wang *et al.*, 2015). In another work a model was presented regarding pharmacokinetics (the drugs dynamics in tissue) and pharmacodynamics (the corresponding effects on their targets) for personalizing computer simulation of mammary gland tumor treatment (Albert *et al.*, 2016). McKenna *et al.* (2018) has presented a computational model for chemotherapy in mammary gland tumor. Another model "Tumor code" (Fredrich *et al.*, 2018) was presented as a simulation framework for vascularized tumors.

Anticancer drugs show varying efficacy for different patients. For the selection of suitable medicine for any patient, oncologists take the decision by their experience and seeing patient's history, tumor grade and stage. In the present study, mammary gland tumor was induced in rat models followed by treatment with TC and AC which are widely used against breast cancer patients in hospitals of our region (Adeel *et al.*, 2019). Using agent-based computer simulation and modeling technique, this study presents a simulation model for TC and AC. It would be helpful for oncologists to decide suitable combination (TC or AC) for cancer treatment by seeing visually (on

computer screen) the agents including TCAL, appropriate drugs administration, affected WBC count, and Hb level. Since SMTA was executed by providing the same drugs administration by which tumor-induced rat models were treated, so some results from SMTA and some results obtained from rat models were compared to validate the presented simulation model. For complete validation of the remaining SMTA results (that could not be obtained from rat models) were compared with published results (Adeel *et al.*, 2019). This model, during its execution, analyzes the visual interactions of the mammary gland tumor cells aggression level, drugs administration, WBC count and Hb level affected by AC and TC.

As discussed earlier, the agents are such components that have adaptive behavior in an autonomous environment under certain varying situations for the solution of a complex problem (Macal, 2016). Under certain rules, these agents interact with each other depending upon their properties. SMTA consists of agents including mammary gland (breast) cells, tumor cells, TC and AC drugs elements, WBC as population, and Hb level. Mammary gland cells have properties including proliferation (birth) and metastasize (mutation). Tumor cells have properties including proliferation (birth), apoptosis (death by time and drugs), and uncontrolled proliferation (mutation/reproduction). TC and AC have same properties including fighting, apoptosis (death) and affecting the proliferation (killing tumor cells). WBC and Hb have same properties including proliferation (birth), apoptosis (death) and affected by drugs. All these agents are shown with their properties in Fig. 1.

MATERIALS AND METHODS

Study design: In this study, mammary gland tumor was induced in 389 rat models using 2.5 mg of N-methyl-N-nitrosourea in 0.2 mL of normal saline (Rajmani *et al.*, 2011) at Institute of Pharmacy, Physiology and Pharmacology, University of Agriculture Faisalabad, Pakistan. Out of 389 cases, 191 rats were treated by chemotherapy with AC for 4 cycles (one cycle consisted of 21 days), and 198 rats received chemotherapy using TC, also for 4 cycles. In TC cohort, a dose of 1.07 mg/m^2 of docetaxel was given in a combination of 8.57 mg/m^2 of cyclophosphamide. Similarly, in AC cohort, 0.85 mg/m^2 of doxorubicin was given with 8.57 mg/m^2 of cyclophosphamide. Hb level and WBC count were recorded from hematology follow-up reports of rat models.

Simulation Model for TC and AC: NetLogo 5.1 (Java-based simulation tool) was used to develop SMTA to analyze the cases with same number of cycles for both TC and AC cohorts observing their Hb level, WBC count, and TCAL. It also analyzes the status of TCAL without any treatment of tumorous subjects.

Formulation of equations for SMTA: The agents' interactions and behaviors may be formalized by using equations (Macal, 2016). Following equations are also used for defining rules involved in developing behavior and interaction among agents of SMTA (Fig. 1).
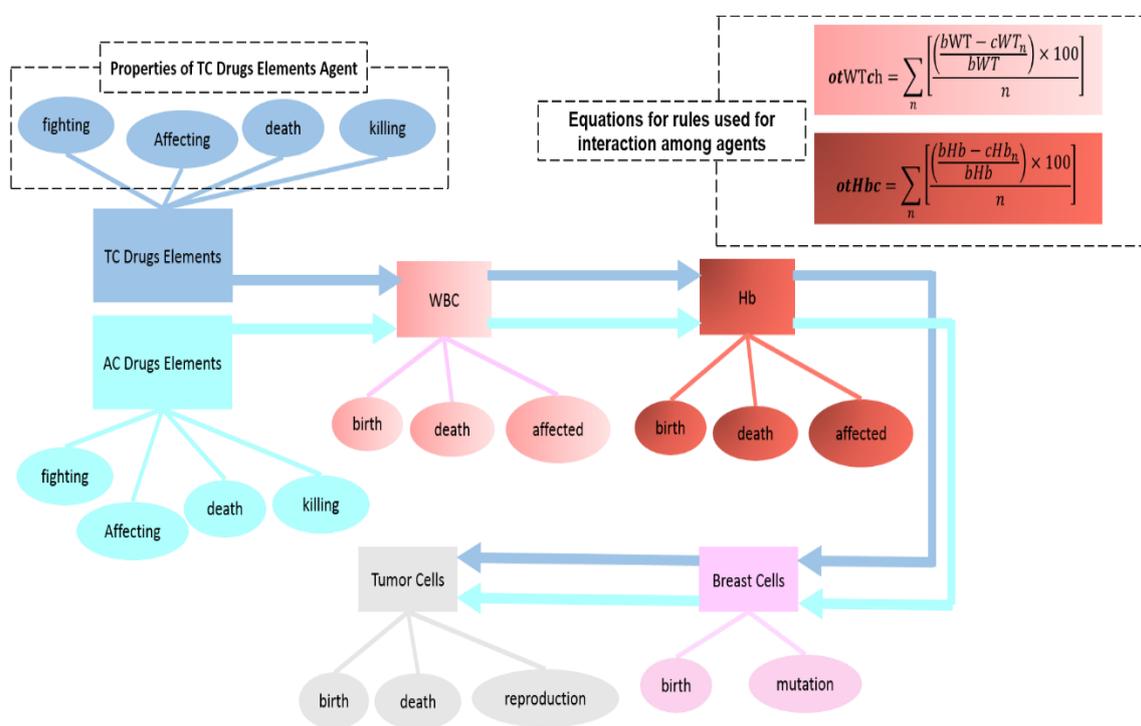
Fig. 1: Simulation model for docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide: a complex system with agents and their properties for adaptive behavior in an autonomous environment, with equations for rules used for interaction among agents (TC, docetaxel plus cyclophosphamide; AC, doxorubicin plus cyclophosphamide; WBC, white blood cells; Hb, hemoglobin; otHbc, overall trend in subjects' hemoglobin change; otWTch, overall trend in the change of count of subjects' WBC; bHb, base value of Hb level; cHb, current value of Hb level; n, chemo cycle no.; bWT, base value of WBC count; cWT, current value of WBC count).

Effect of TC and AC on Hb and WBC count: The overall trend in subjects' Hb change, denoted by otHbc was calculated by already derived equation (Adeel *et al.,* 2019):

$$otHbc = \sum_n \left[\frac{\left(\frac{bHb - cHb_n}{bHb}\right) \times 100}{n} \right] \qquad (1)$$

where *bHb* is base Hb for providing an initial value, which was obtained before chemo, *cHb* is for the current value of Hb which was obtained after the first chemo cycle for example, before second, third, or fourth chemotherapy cycle and n is 1st, 2nd, 3rd, or 4th cycle of chemotherapy.

Following equation is derived that calculates the overall trend in the change of count of subjects' WBC, denoted by otWTch:

$$otWTch = \sum_n \left[\frac{\left(\frac{bWT - cWT_n}{bWT}\right) \times 100}{n} \right] \qquad (2)$$

where *bWT* is base value of the count of WBC for providing initial value, which was obtained before chemo, *cWT* is for current value of the count of WBC which was obtained after the first chemo cycle for example, before second, third, or fourth chemotherapy cycle, and *n* is 1st, 2nd, 3rd, or 4th cycle of chemotherapy.

Designing of a computer algorithm for SMTA and its coding were developed based upon the rules derived by Equation 1 & 2 for the interaction of properties of SMTA agents.

Statistical analysis: Two tests including two-sample t-test and paired t-test were applied using Minitab 17 for analysis of the results obtained using Equation 1 and Equation 2 for observing both otHbc and otWTch (by TC and AC). Two-sample t-test, at α=0.05, was applied for statistical analysis of the results obtained from rat models. Whereas, for validation, paired t-test was then used to compare the results obtained from SMTA with rat models analytical results.

RESULTS

Execution of SMTA: This model was executed with the obtained inputs from test reports of rat models. SMTA received the same drugs administration as given to rat models. This execution provided the visual exploration of the interactions of TC and AC against TCAL leading to variations in Hb level and WBC count. The interface of SMTA is divided into four quarters: Quarter-I for WBC and normal mammary gland cells, Quarter-II for WBC and mammary gland with tumor cells without any treatment, Quarter-III for WBC and mammary gland with tumor cells for chemotherapy with TC, and Quarter-IV for WBC and mammary gland with tumor cells for chemotherapy with AC as shown in Fig. 2a.

With the execution of SMTA, tumor size, as shown in Quarter-II, starts spreading and at the end of cycle 4 it was increased due to the absence of any treatment. WBC count was lowered at each cycle as shown in Quarter-III and IV because of TC and AC respectively. Tumor size also gets smaller at each cycle as shown in Quarter-III and IV and finally becomes very small on the completion of chemotherapy. All these quarters for the status of cycles 1 to 4 are shown in Fig. 2b-2e.
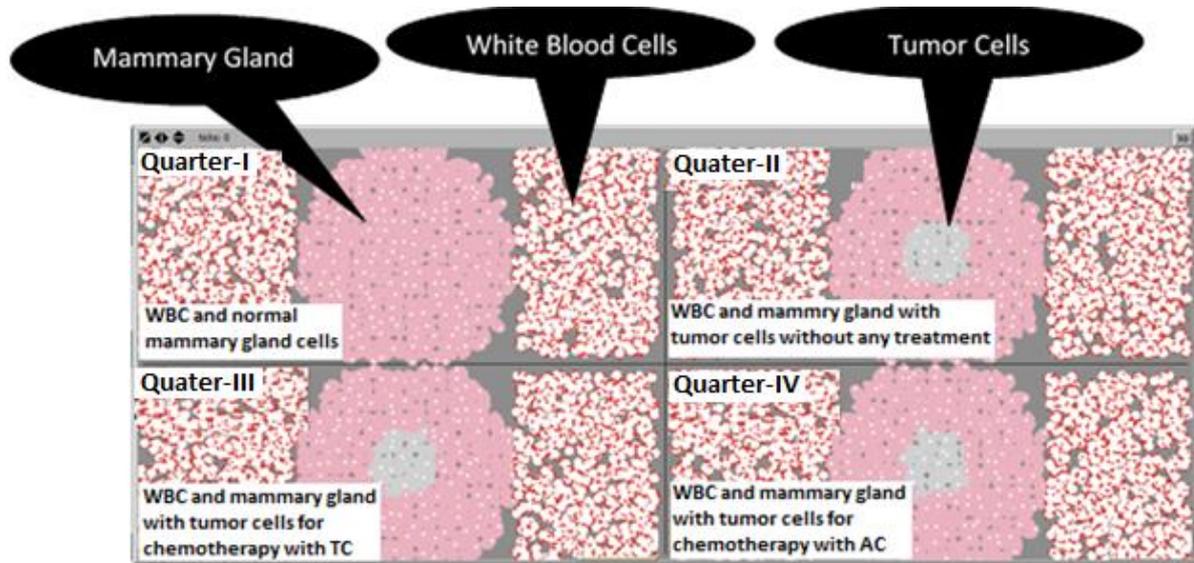
Fig. 2a: Four quarters of simulation model for docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide (TC, docetaxel plus cyclophosphamide; AC, doxorubicin plus cyclophosphamide).
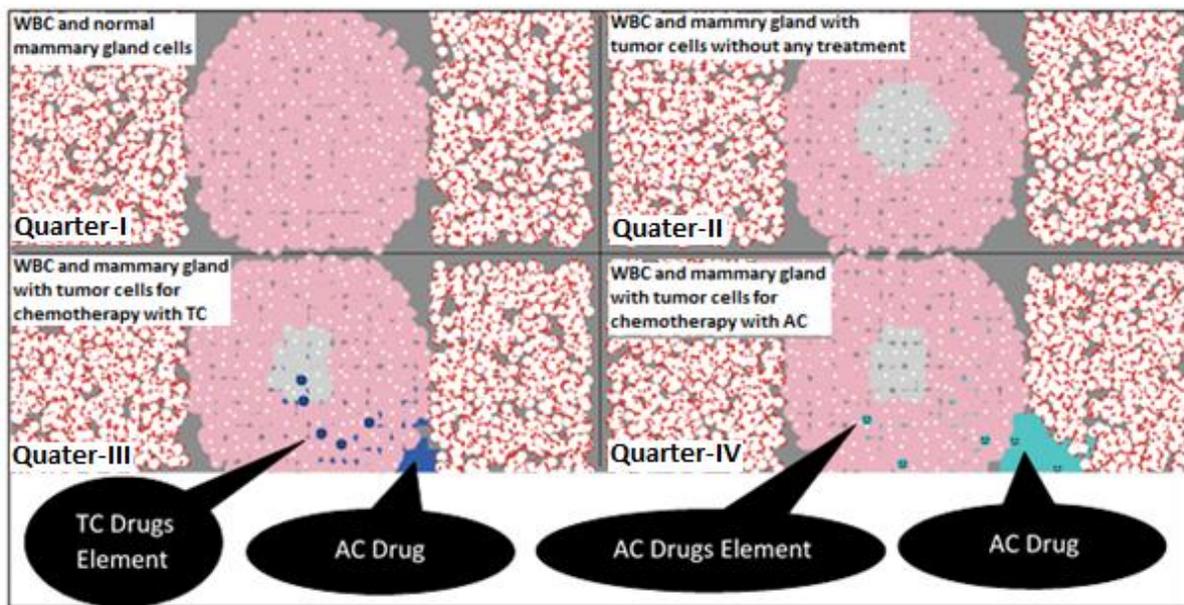
Fig. 2b: The status of Quarter-II, Quarter-III, and Quarter-IV during cycle 1 of chemotherapy with docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide drugs (TC, docetaxel plus cyclophosphamide; AC, doxorubicin plus cyclophosphamide).
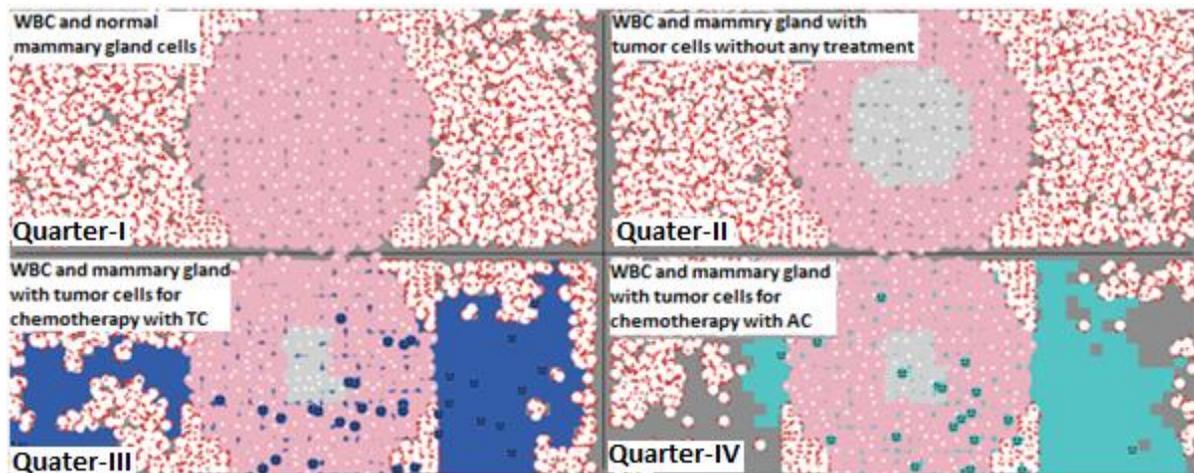
Fig. 2c: The status of Quarter-II, Quarter-III, and Quarter-IV during cycle 2 of chemotherapy with docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide drugs (TC, docetaxel plus cyclophosphamide; AC, doxorubicin plus cyclophosphamide).
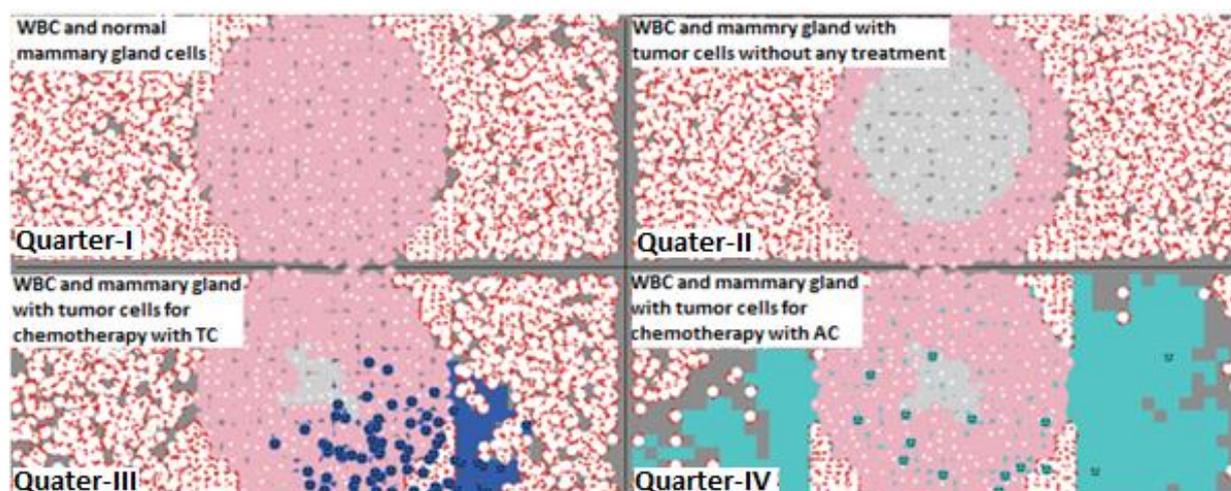
Fig. 2d: The status of Quarter-II, Quarter-III, and Quarter-IV during cycle 3 of chemotherapy with docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide drugs (TC, docetaxel plus cyclophosphamide; AC, doxorubicin plus cyclophosphamide).
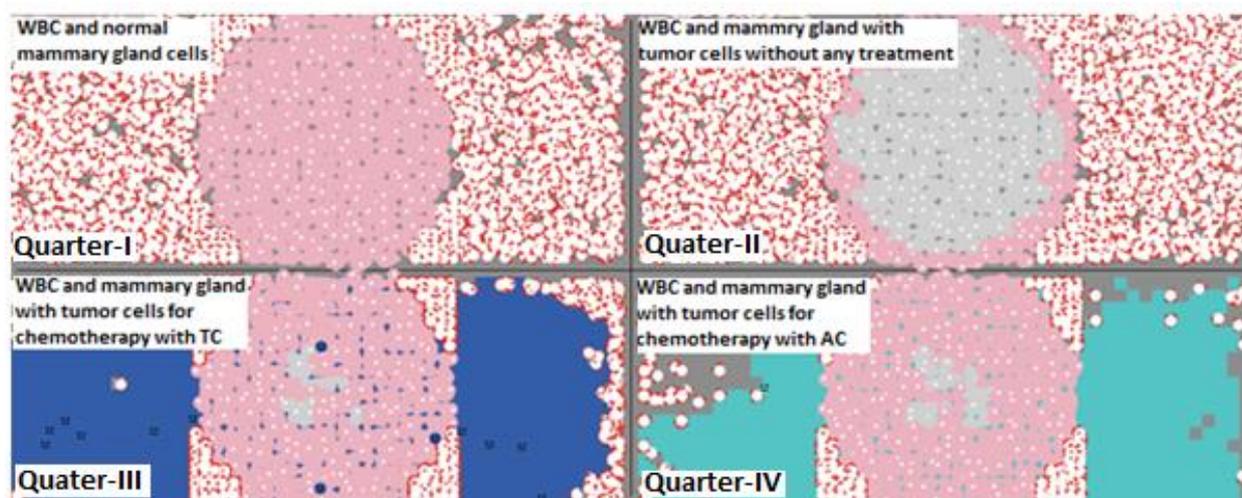
Fig. 2e: The status of Quarter-II, Quarter-III, and Quarter-IV during cycle 4 of chemotherapy with docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide drugs (TC, docetaxel plus cyclophosphamide; AC, doxorubicin plus cyclophosphamide).

SMTA was executed from cycle 1 to 4 for 198 cases with the same drugs administration with TC given to rat models to obtain the simulation results of tumor cells proliferation in percentage, WBC count and Hb level. Similarly, SMTA was executed from cycle 1 to 4 for 191 cases with the same drugs administration with AC given to rat models to obtain the simulation results of tumor cells proliferation in percentage, WBC count and Hb level.

Results of the interaction of TC and AC with TCAL
Two-Sample T-Test for overall trend of change in Hb level by TC and AC: Equation 1 is applied to calculate "overall trend of change in Hb level". Lists of values of "change in Hb level" of two cohorts (of 198 cases treated by TC and 191 cases treated by AC) were prepared using Hb level from the pathological reports of rat models on first chemo cycle and Hb level on the concurrent chemo cycle of the same cases. A two-sample t-test was applied and results are mentioned in Table 1. Analyzing rat models, there was statistically significant difference between the overall changes in Hb level affected by TC as compared to AC. Since P-value=0.000<0.05 (significance

level), Hb level was affected 3.98% more by TC than AC, with 95% CI for the difference of 3.107 and 4.842.

Similarly, the same analysis was performed for all values of "change in Hb level" obtained from SMTA. It was observed that the averages of "change in Hb level" values of 198 TC and 191 AC cases were 9.12% and 5.00 % respectively.

Two-Sample T-Test for overall trend of change in WBC count by TC and AC: Equation 1 is applied to calculate "overall trend of change in WBC count". Lists of values of "change in WBC count" of two cohorts (of 198 cases treated by TC and 191 cases treated by AC) were prepared using WBC count from the pathological reports of rat models on first chemo cycle and WBC count on the concurrent chemo cycle of the same cases. A two-sample t-test was applied and results are mentioned in Table 1. Analyzing rat models, there was a statistically significant difference between the overall changes in WBC count affected by TC as compared to AC. Since P-value=0.000<0.05, WBC count was affected 5.13% more by TC than AC, with 95% CI for the difference of 2.82 and 7.44.

Table 1: Statistical analysis of the results obtained from hematology follow-up reports of rat models for validating the results from simulation model for docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide

Two-Sample T-Test for overall trend of change in Hb level by TC and AC

	N	Mean	StDev	SE Mean
otHbc by TC	198	9.07	5.16	0.37
otHbc by AC	191	5.10	3.38	0.24

Difference = μ (otHbc by TC) - μ (otHbc by AC)

Estimate for difference: 3.975
95% CI for difference: (3.107, 4.842)

T-Test of difference = 0 (vs ≠): T-Value = 9.01   P-Value = 0.000   DF = 341

Two-Sample T-Test for overall trend of change in WBC count by TC and AC

	N	Mean	StDev	SE Mean
otWTch by TC	198	30.8	12.2	0.87
otWTch by AC	191	25.7	10.9	0.79

Difference = μ (otWTch by TC) - μ (otWTch by AC)

Estimate for difference: 5.13
95% CI for difference: (2.82, 7.44)

T-Test of difference = 0 (vs ≠): T-Value = 4.37   P-Value = 0.000   DF = 384

Paired T-Test for validation of "overall trend of change in Hb level" from rat models and SMTA

	N	Mean	StDev	SE Mean
Means of OtHbc from rat models	2	7.09	2.81	1.99
Means of OtHbc from SMTA	2	7.06	2.91	2.06
Difference	2	0.0250	0.1061	0.0750
95% CI for mean difference:	(-0.9280, 0.9780)			

T-Test of mean difference = 0 (vs ≠ 0): T-Value = 0.33   P-Value = 0.795

Paired T-Test for validation of "overall trend of change in WBC count" from rat models and SMTA

	N	Mean	StDev	SE Mean
Means of OtWTch from rat models	2	28.25	3.61	2.55
Means of OtWTch from SMTA	2	27.35	2.76	1.95
Difference	2	0.900	0.849	0.600
95% CI for mean difference:	(-6.724, 8.524)			

T-Test of mean difference = 0 (vs ≠ 0): T-Value = 1.50   P-Value = 0.374

(TC, docetaxel plus cyclophosphamide; AC, doxorubicin plus cyclophosphamide; WBC, white blood cells: otHbc, overall trend in subjects' hemoglobin change; otWTch, overall trend in the change of count of subjects' WBC; SMTA, simulation model for TC and AC).
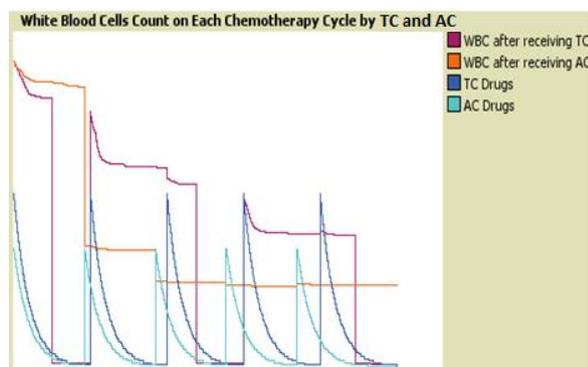
Fig. 3: The status of white blood cells counts affected during four cycles of chemotherapy with docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide drugs (TC, docetaxel plus cyclophosphamide; AC, doxorubicin plus cyclophosphamide; WBC, white blood cell).
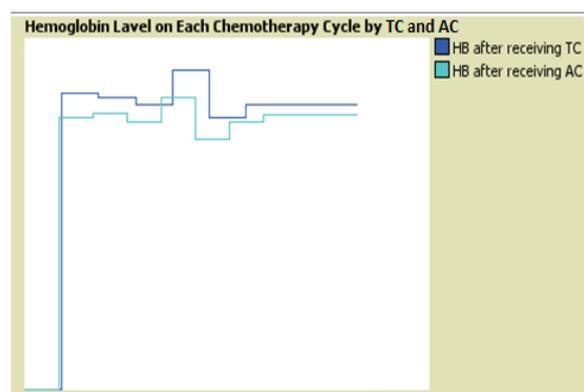
Fig. 4: The status of hemoglobin level affected during four cycles of chemotherapy with docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide drugs (TC, docetaxel plus cyclophosphamide; AC, doxorubicin plus cyclophosphamide; Hb, hemoglobin).

Similarly, the same analysis was performed for all values of "change in WBC count" obtained from SMTA. It was observed that averages of "change in WBC count" values of 198 TC and 191 AC cases were 29.3 and 25.4% respectively as shown in Table 1.

Providing SMTA with same drugs administration as given to rat model cohorts, average values of TCAL were observed to be 28.1 and 24.3% for TC and AC respectively. Thus, the restriction of tumor cells proliferation was 3.8% higher by AC than TC as shown in Table 1.

DISCUSSION

This study is carried out for two combinations of chemotherapy including TC and AC, as discussed in our earlier work (Adeel *et al.*, 2019). To calculate "overall trend of change in WBC count", Equation 2 was derived on the basis of a reported equation (Equation 1) (Adeel *et al.*, 2019). Equation 1 was used to calculate "overall trend of change in Hb level". Using these equations, rules were programmed for the interactions among SMTA agents (Fig. 1) on tumor mammary gland cells, WBC count, Hb level and efficacy of anticancer drugs (TC and AC). Their interactions were then observed in three ways: (i) without any treatment (ii) treatment with TC (iii) treatment with AC. Results revealed that AC remained better in efficacy as compared to TC for controlling TCAL with least toxic effect on WBC count and Hb level. WBC status and life of drug elements are shown in Fig. 3. These results are obtained by execution of SMTA for all the four cycles of chemotherapy. Fig. 4 shows the Hb level affected by both combinations during four chemo-cycles.

From the results, it is concluded that during drugs administration, TCAL varied from one individual to another. This variation might be caused by different factors including the efficacy of antitumor drugs, subject's immune system, tumor resistance and tumor biomarkers.

Moreover, using agent-based modeling and simulation, it has been established by the community that the complex behavior of agents in complex systems is adaptive and autonomous (Wang *et al.*, 2015; Macal, 2016; Hosseini and Naghavi, 2017; Jayasekera *et al.*, 2018; Norton *et al.*, 2019). The current study proves this concept practically by determining the agents of SMTA. These agents showed complex adaptive behavior with their properties mentioned in Fig. 1 when interacting with one another with different input values during execution of SMTA. Drugs elements of TC and AC were provided in SMTA to kill cancer cells, but they affected WBC count and Hb level, before reaching their targets. When WBC count and Hb level becomes lower than the normal values, it causes a disturbance in the immune response of the subjects (Costa *et al.*, 2019) and consequently drugs resistance becomes low (Meng *et al.*, 2019). On the other side, normal breast cells transformed into tumor cells due to cellular mutation and aggressive behavior (Ayob and Ramasamy, 2018).

The validation of results: Comparable computer simulation agent-based model like SMTA could not be found in literature. Therefore, to validate the results of this study "overall trend of change in Hb level" and "overall trend of change in WBC count" of SMTA and rat models were compared with each other. "Overall trend of change in Hb level" was compared with the validated and published results (Adeel *et al.*, 2019). It was observed that statistically (applying paired t-test) there was no significant difference between means of "overall trend of change in Hb level" observed form SMTA and rat models because p-value = 0.795>0.05. Similarly, there was statistically no significant difference between means of "overall trend of change in WBC count" observed form SMTA and rat models because p-value = 0.374>0.05, as shown in Table 1.

Conclusion and Future Work: Results showed that AC remained better in efficacy than TC in controlling TCAL with a least toxic effect on WBC count and Hb level. It is also concluded that the TCAL, during drugs administration, varied from case to case. Moreover, the agents in agent-based simulation model (like SMTA) showed complex adaptive behavior with their properties when interacting with one another with different input values during its execution.

The proposed simulation model, SMTA was developed with the intention of learning and showing possible benefits for its application in clinical oncology. The enhancement in SMTA may be used to predict the drug dose dependent performance.

Author contributions: MA, MNF, and MA conceived and designed the study. MA, MNF, SA, MA and WM performed experiments and analyzed results from rat models. MA and MA executed and analyzed the simulation experiments. All authors compiled the data, technically revised the manuscript and approved the final version.

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