RESEARCH ARTICLE

ROLE OF NANOTECHNOLOGY IN EPIRUCIBIN FOR BREAST CANCER THERAPY IN TAIF CITY

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Department of Pharmacy, clinical Pharmacy, Taif University, Saudi Arabia.

Abstract

Background: According to Breast Cancer Screening Programs in 26 Countries, 19.0% of females have breast cancer. The aim of our study is assessing the role of nanotechnology in breast cancer therapy. Epirubicin drug was selected as an example of the pharmaceutical nanosystem.

Method: A cross sectional study was conducted among 300 women in Taif city and the data were collected using a self-administered questionnaire. The questionnaire determines the knowledge of risk factors and the disease stages (breast cancer). The patients also interviewed to determine the duration, the response and the feeling of any harmful symptoms after using of Epirubicin in the therapy. The answers were scored; frequencies and percentages were used for describing data. Chi-square test and a P value of (0.05) were used to determine the significant association between the participants' variables.

Results: Most patients respondents were between 21 to above 70 years old. About 28.1% breast cancer patients discover the disease by the chance, while 46.9% by self-examination. 43.75% of breast cancer patients use Epirubicin drug. The effectiveness of therapy takes about 3-9 months. 15.6% only have a serious common side effect and 18.7% have any side effect. Therefore the number of patients who accepted the therapy by Epirubicin was 78.6%

Conclusion: Participants had poor knowledge about the disease and management. Using Epirubicin had a good attitude in managing time and compliance of the disease. The nanoparticle system presented in Epirubicin drug considers the solving of most common patient incompliance.

Introduction:-

The body is made up of trillions of living cells. Normal body cells grow, divide to make new cells, and die in an orderly way (apoptosis). During the early years of person’s life, normal cells divide fastest to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

When abnormal cell growth occurs with the potential to invade or spread to other parts of the body, these cells are called cancerous cells. Fig. I-1. It's become cancer cells because of DNA damage. When DNA is damaged, the cell either repairs the damage or

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damageordies. In cancer cells, the damaged DNA is not repaired, but the cell doesn’t die like it should. Instead, the cell goes on making new cells that the body doesn’t need. These cells are called cancer cells. In most cases, the cancer cells form a tumor. Over time, the tumors can replace normal tissue, crowd it, or push it aside (2).

![Diagram of normal cell and cancer cell growth](image)

**Fig I-I:** Normal cell and cancer cell growth

Cancer remains one of the most common causes of mortality in the world. According to the Cancer Incidence Report Saudi Arabia 2010 and Saudi Cancer Registry, cancer is one of the leading causes of death in KSA. About 13,706 cases of cancer patients were in KSA. The breast cancer is the most prevalent and the most common, which ranked first by 27.4% in Fig (I-II) (3).

![Mortality of cancer among KSA population, 2010](image)

**Fig I-II:** Mortality of cancer among KSA population, 2010

And according to Breast Cancer Screening Programs in 26 Countries, 2012: Organization, Policies, and Program Reach when screened 6200 in KSA; 19.0% of females have breast cancer (4).

Breast cancer begins in the breast tissue that is made up of glands for milk production, called lobules, and the ducts that connect the lobules to the nipple. The remainder of the breast is made up of fatty, connective, and lymphatic tissues.

Breast cancer may be Ductal carcinoma in situ (DCI) or non-invasive breast cancer which they are abnormal cells. The atypical cells have not spread outside of the ducts into the surrounding breast tissue. Ductal carcinoma in situ is very early cancer that is highly treatable, but if it’s left untreated or undetected, it can spread into the surrounding breast tissue (Fig. I-III) (5,6).
Another type of breast cancer is invasive ductal carcinoma, in which the cancerous cells break through the ductal or glandular walls into surrounding breast tissues and spread to other parts of the body. Fig. IV:

It's considered the most pronounced type and it's dangerous on its stage.

Especially, the prognosis of invasive breast cancer is strongly influenced by the stage of the disease. Cancer has many stages, Stage I: This is usually a small cancer or tumor that hasn't grown deeply into nearby tissues and hasn't spread to the lymph nodes or other parts of the body. It is often called early stage cancer. Stage II and III: These stages indicate cancer or tumor that are larger in size, have grown more deeply into nearby tissues, and have spread to lymph nodes, but not to other parts of the body. Stage IV: this stage means that the cancer has spread to other organs or parts of the body. It may also be called advanced or metastatic cancer. Fig (I-IV) (7).

(A) Normal duct (B) ductal carcinoma in situ (DCIS)

Fig I-III: Ductal Carcinoma In Situ.
There are many factors that help in increasing the probability of the breast cancer disease. There are many studies to determine them. According to American cancer society risk of developing breast cancer increases as getting older. About 1 out of 8 invasive breast cancer are found in women younger than 45, while about 2 of 3 invasive breast cancer are found in women age 55 or older (8).

About 5% to 10% of breast cancer cases are thought to be hereditary, meaning that they result directly from gene defects (called mutations) inherited from a parent. Breast cancer risk is higher among women whose close blood relatives have this disease, less than 15% of women with breast cancer have a family member with this disease. This means that most (over 85%) women who get breast cancer do not have a family history of this disease. The probability in a woman whose mother has had breast cancer is 2 to 4 times increased risk of developing new cancer in the other breast or in other part of the same breast (9).

According to American Institute for Cancer Research and World Cancer Research Fund lifestyle is the major cause of cancer related illness. This finding was expressed after examining people across the globe and looking at half a million cancer related studies. They found that 60% of cancer can be attributed to lifestyle choices of smoking, poor diet, and obesity.

Changes in hormone levels can interfere with the process and that can lead to cancer, the exposure to toxic chemicals in our daily lives from wide range of sources can increase cancer risk, sunlight, radiation, and infectious agent (bacteria, virus) can cause cancer, while the hereditary factors account for 6% of cases (10).

Cancer therapy:-
Cancer treatment is currently a major focus of investigation which have many treatment option that include surgery, radiation therapy, chemotherapy and targeted therapy.

Treatments decisions are made by the patient and the physician after consideration of the optimal treatment available for the stage and biological characteristics of the cancer, the patient’s age and preferences, and the risks and benefits associated with each treatment protocol.

Treatments like radiation and surgery are considered local treatments, they act on the infected area such as the breast, lung, and prostate. However, they targeted the cancerous cells directly.

Because of that chemotherapy is the doctor choice in case of spreading cancer.

Chemotherapy is one of the most common ways in cancer treatment. Chemotherapy is using specific chemical agents or drugs that are destructive to malignant cells and tissues in order to cure patients. Chemotherapy cannot differentiate between normal cells and cancer cells. Which means the chemotherapy targets cells whether normal or cancerous cells. The later lead to harm the healthy cells which have a high rate of growth and multiplication include cells of the bone marrow, hair, GI mucosa, and skin. The side effects may be caused by cardiotoxicity and pulmonary fibrosis. Severity of side effects varies between drugs (11).

There are other ways for treatment as exercise. Exercise is an effective intervention to improve quality of life, cardiorespiratory fitness, physical functioning, and fatigue in breast cancer patients and survivors. Larger trials that have great focus on quality and adverse effects demonstrate long-term benefits of exercise intervention. Pre- to post-test analysis revealed that women who exercised had significantly less depression, state and trait anxiety over time compared to controls. After the crossover, the control group demonstrated comparable improvement in both depressive and state anxiety scores. Self-esteem did not change significantly. Subjects who received exercise recommendations from their physician exercised significantly more than subjects who received no recommendation (12).

Researchers worldwide have been searching for an optimal cancer treatment without afflicting significant morbidity. Recent advances in cancer nanotechnology provide a new horizon for cancer treatment.
chnology have raised exciting opportunities for specific drug delivery by an emerging class of nanotherapeutics that may be targeted to specific plastic cellsonly (13).

Several nanoparticle technologies are currently progressed to clinical use. Currently, FDA approved some drug products employing this technology Table I-I.

<table>
<thead>
<tr>
<th>Table I-I:</th>
<th>FDA approved some drug products employing this technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Sponsor</td>
</tr>
<tr>
<td>Megace ES</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Abraxane</td>
<td>APP</td>
</tr>
<tr>
<td>Doxil</td>
<td>Alza Corporation</td>
</tr>
<tr>
<td>Emend</td>
<td>Merck &amp; Co.</td>
</tr>
<tr>
<td>TriCor</td>
<td>Abbott Laboratories</td>
</tr>
<tr>
<td>Estrasorb</td>
<td>Novavax, Inc.</td>
</tr>
<tr>
<td>Rapamune</td>
<td>Wyeth</td>
</tr>
<tr>
<td>Articoat</td>
<td>Smith &amp; Nephew</td>
</tr>
<tr>
<td>Zirconium oxide</td>
<td>Altana Nanotechnologies, Inc.</td>
</tr>
</tbody>
</table>

One of these technologies is Carbon nanotubes. Carbon nanotubes are hexagonal networks of carbon atoms, 1 nm in diameter and 1–100 nm in length, as a layer of graphite rolled up into a cylinder. There are two types of nanotubes: single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs) as represented in Fig VI which differ in the arrangement of their graphitic cylinders. These are small macromolecules that are unique for their size, shape, and have remarkable physical properties (15).

Some distinct advantages of carbon nanotubes over other drug delivery and diagnostic systems were their very interesting physicochemical properties such as ordered structure with high aspect ratio, ultra-light weight, high mechanical strength, high electrical conductivity, high thermal conductivity, metallic or semi-metallic behavior and high surface area (16).

Epirubicin is a drug depending on MWNTs, The Combination chemotherapy and Nanoparticle drug delivery are two areas that have shown significant promise in cancer treatment. Combined therapy of two or more drugs promotes synergism among the different drugs against cancer cells and suppresses drug resistance through distinct mechanisms of action. Nanoparticle drug delivery, on the other hand, enhances therapeutic effectiveness and reduces side effects of the drug payloads by improving their pharmacokinetics.

Multi-wall nanotubes (MWNTs) are coaxial assembly of SWNTs have diameter close to 5nm to 50 nm, The interlayer distance in MWNT is close to the distance between graphenelayers in graphite (17) Fig (I-VI).

Epirubicin is an Anthracycline drug used for chemotherapy. It can be used in combination with other medications to treat breast cancer. Anthracyclines are considered to be among the most active available agents to treat breast cancer and have become core components of adjuvant regimens. Epirubicin-taxanes combinations are active in treating breast cancer and do not appear to be associated with any pharmacokinetic interactions.

According to table I-II Epirubicin Hydrochloride use MWNTs (Fig. I-VI-B) technology which are layers of graphite with an enormous surface area and an excellent electronic and thermal conductivity (18).
Table I-II: Carbon Nanotube as DDS

<table>
<thead>
<tr>
<th>Type of nanotubes</th>
<th>Drug</th>
<th>Method of immobilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>MWCNTs</td>
<td>Cisplatin</td>
<td>Encapsulation via capillary forces</td>
</tr>
<tr>
<td>f-CNTs</td>
<td>Amphotericin B</td>
<td>Conjugated to carbon nanotubes</td>
</tr>
<tr>
<td>SWCNTs</td>
<td>Gemcitabine</td>
<td>Encapsulation</td>
</tr>
<tr>
<td>MWNTs</td>
<td>Epirubicin hydrochloride</td>
<td>Adsorption</td>
</tr>
<tr>
<td>MWCNTs@poly(ethylene glycol-b-propylene sulfide)</td>
<td>Doxorubicin</td>
<td>Adsorption</td>
</tr>
<tr>
<td>f-CNTs</td>
<td>Sulfamethoxazole</td>
<td>Adsorption</td>
</tr>
<tr>
<td>SWNTs-PL-PEG-NH₂</td>
<td>Pt(IV) prodrug FA</td>
<td>Covalent amide linkages</td>
</tr>
<tr>
<td>SWNTs</td>
<td>Cisplatin – EGF</td>
<td>Attachment to carbon nanotubes via amide linkages</td>
</tr>
<tr>
<td>MWCNTs</td>
<td>Dexamethasone</td>
<td>Encapsulation</td>
</tr>
</tbody>
</table>

MWCNTs multi walled carbon nanotubes; f-CNTs functionalized carbon nanotubes; SWNTs-PL-PEG-NH₂ amine-functionalized single-walled carbon nanotubes.

Epirubicin acts by intercalating DNA strands. Intercalation results in complex formation which inhibits DNA and RNA synthesis. It also triggers DNA cleavage by topoisomerase II, resulting in cell death. Binding to cell membranes and plasma proteins may be involved in the compound's cytotoxic effects. Epirubicin also generates free radicals that cause cell and DNA damage. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicals. The anti-proliferative and cytotoxic activity of Epirubicin is thought to result from these or other possible mechanisms. All these mechanisms improve its anticancer activity.

Epirubicin Hydrochloride for Injection is an Anthracycline cytotoxic agent, intended for intravenous administration. Epirubicin Hydrochloride for Injection is supplied as a sterile, orange-red, lyophilized powder in single-dose vials containing 50 mg or 200 mg of Epirubicin hydrochloride. Each 50 mg and 200 mg vial contains 250 mg and 1000 mg inactive ingredient, lactose, respectively.

Following intravenous administration, Epirubicin is rapidly and widely distributed into the tissues. Binding of Epirubicin to plasma proteins, predominantly albumin, is about 77% and is not affected by drug concentration. Epirubicin also appears to concentrate in red blood cells; whole blood concentrations are approximately twice those of plasma.

(a)Singlewalled(SWNTs)  
(b)Multiwalled(MWNTs)  
Fig I-VI. Carbon nanotubes
Epirubicin is extensively and rapidly metabolized by the liver and is also metabolized by other organs and cells, including red blood cells. Epirubicin and its major metabolites are eliminated through biliary excretion and, to a lesser extent, by urinary excretion. Common side effects; Nausea, vomiting, diarrhea, abdominal pain, flushing, or skin/nail color changes may occur, Temporary hair loss. Serious side effects; bone marrow suppression; including leucopenia, thrombocytopenia and anemia, Myocardial toxicity; including heart failure (23).

Management:-
- Measurements of CBC, ECG, Liver function test, serum creatinine, and electrolytes
- Premedication with an antiemetic may be useful because Epirubicin is emetogenic.
- Infusion site must be monitored closely to prevent extravasations; sever local tissue necrosis will result if extravasations occur.
- Monitor for acute nausea, vomiting, anemia, infection, bleeding, and cardiotoxicity (24).

The aim of our study is to determine the prevalence of breast cancer in Taif city. Also, we study the risk factors which increase the prevalence of the disease. Most studies were done on European women. We do our study on Saudi women as all risk factors were variable. We also try to assess the role of nanotechnology in breast cancer therapy. Epirubicin drug was selected as an example of the pharmaceutical nanosystem which is very effective in breast cancer therapy.

Methodology and Design:-
Purpose and Research Objectives:-
- The primary purpose is to determine the prevalence of breast cancer in Taif city.
- The secondary purpose is to determine the role of nanotechnology in breast cancer therapy.
- The third is to determine the efficacy of Epirubicin drug in breast cancer therapy.

Setting:-
The oncology and pharmacy department of the hospital.

Study Design:-
Across-sectional study allocated for breast cancer female patient, to determine the role of nanotechnology in breast cancer therapy during the period from September 2014 till December 2015.

Settings and Duration:-
The study was conducted in the departments of oncology and pharmacy of the hospital. The study was carried out for over a year (From September 2014 till December 2015).

Sample Volume and Selection:-
A sample composed of 300 women in Taif city, ages were between 21 to above 70 years old.

Tool of data collection:-
A structured questionnaire was designed for data collection by the researchers based on review of literature. It includes three parts, The first part: the socio-demographic data, such as: age; residency, occupation, age at menarche, marital status; age of bearing the first baby and the age of married as the later increases the probability of breast cancer.

The second part: the way of discovering the disease and the risk factors increase the prevalence of breast cancer.

The third part: type of treatment that patient has, like; radiation therapy, chemotherapy or surgery. Also the effect of using Epirubicin in her therapy or not was studied.

The role of nanotechnology in treatment appears by using Epirubicin as a model drug. We study the effectiveness of using this drug in enhancing the therapy, and reducing or inhibition any side effects from the therapy.

Method:-
We conducted cross-sectional study, the data was collected from face to face interview and the patient files presented in oncology department or computerized in patients files of the hospital. Data also collected by asking nurses,
doctors and pharmacists. All are answered the questionnaire and their answers were collected. All data has been statistically analysis to specify a recommended answer.

Ethical considerations:-
Official permission on this study was obtained from the previous sponsors. Hospital, doctors, nurse and pharmacist were informed about the nature of the study. Oral consent obtained from doctors, nurse and pharmacist who agreed to participate in the study. We accessed patients’ files from the pharmacy department after an official permission.

Inclusion criteria:-
- Adult female no matter the nationality
- Female patients with breast cancer
- Age between 21 years and above 70 years.
- No matter any other disease condition
- Patient using Epirubicin in there therapy
- New or recurrence case
- Benign or malignant tumors.

Exclusion criteria:-
- Female patient under 21 years old
- Non-breast cancer patients
- Male cancer patient
- Pregnant and nursing women
- Patient who are not using Epirubicin in there therapy.

Statistical Analysis:-
All data in this study are expressed in the form of mean. Frequencies and percentages were used for describing data, chi-square test was used with a significance level of $P<0.05$. Statistical analysis was used to determine the prevalence of breast cancer in Taif city, and role of nanoparticles in Epirubicin in breast cancer therapy by measuring the efficacy and harms of the drug.

Research end point:-
The primary end point: was the effectiveness of the drug in the therapy
Secondary end point:-
1. Reducing the most common side effect
2. Frequencies of the patient hospital income

Results and Discussions:-
This study aimed to assess the prevalence of breast cancer in Taif city and to determine the role of nanotechnology in Epirubicin drug in breast cancer therapy. A cross-sectional study was conducted among 300 women in Taif city. Data were collected using a self-administered questionnaire which included questions about the socio-demographic data, knowledge of risk factors that may cause the breast cancer, way of discovering the disease, kind of therapy that the patient received, use of Epirubicin drug in therapy, duration and response of therapy and if the patient feels any harm symptoms.

The prevalence of the breast cancer in Taif city:-
Three hundred participants were interviewed in this study. Males were excluded from that survey. The breast cancer was more predominant in female patients. Also, the breast cancer patients only are included in the survey. Only 32 women have breast cancer in the period of the study (September 2014 till December 2015) were taking their medication in the hospital (From September 2014 and followed up the patient condition until December 2015). The percent of the breast cancer women is more than 10% in 15 months from September 2014 till December 2015. This result was approximately matched with the result of cancer centers survey which found that approximately 12.3 percent of women will be diagnosed with breast cancer at based on 2009-2011 data. For this reason, the World Health Organization considered breast cancer, one of the most important causes of death in women (25).
Demographics:
Sample distribution by age variable:
There was a variation in the interviewed age group. The data were illustrated in Table 1-A and Figure 1-A. The highest percentage of women with breast cancer are in the age group (41-50), they reached up to 31.3%, while the lowest percentage was at the age group (>70%), which reached (9.4%). That indicates that women between age 41-50 years old are more susceptible to the disease from others. Statistical analysis found that there was no significant increase in the risk observed in the adult age and younger age women. These results agree with the previously reported by Ahmedin Jemal, 2007 et al and Shahbazi R, 2015 et al (26, 27).

Table 1-A: Sample distribution by age variable

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of Patients</th>
<th>Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-30</td>
<td>4</td>
<td>12.5 %</td>
</tr>
<tr>
<td>31-40</td>
<td>5</td>
<td>15.6 %</td>
</tr>
<tr>
<td>41-50</td>
<td>10</td>
<td>31.3 %</td>
</tr>
<tr>
<td>51-60</td>
<td>5</td>
<td>15.6 %</td>
</tr>
<tr>
<td>61-70</td>
<td>5</td>
<td>15.6 %</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>3</td>
<td>9.4 %</td>
</tr>
<tr>
<td>total</td>
<td>32</td>
<td>100%</td>
</tr>
</tbody>
</table>

Distribution of the sample by marital status:
Table 2-A and Figure 2-A show that the majority of the respondents were married women, amounting to (68.8%). From the results, we suggest that married women are more susceptible to breast cancer than single ones. Croft L, 2014 et al also found that those who are married have higher optimism scores than their unmarried ones (28).

Table 2-A: Distribution of the sample by marital status

<table>
<thead>
<tr>
<th>Marital Status</th>
<th>Number</th>
<th>Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>married</td>
<td>22</td>
<td>68.8 %</td>
</tr>
<tr>
<td>single</td>
<td>5</td>
<td>15.6 %</td>
</tr>
<tr>
<td>Absolute</td>
<td>1</td>
<td>3.1 %</td>
</tr>
<tr>
<td>Widow</td>
<td>4</td>
<td>12.5 %</td>
</tr>
<tr>
<td>total</td>
<td>32</td>
<td>100%</td>
</tr>
</tbody>
</table>

Distribution of sample by variable profession
Supreme percentage of women with breast cancer in the sample; 43.7% washousewives. The lowest percentage is students, reaching to 18.6 %, as shown in Table 3-A and Figure 3-A. The lack of movement is likely to be an important factor in increasing of breast cancer. Women have to go outdoors at least an hour a day because walking helps to renew the body's cells (29).
The results were shown in Table 4-A represent the effect of pregnancy on the prevalence of breast cancer. The highest percentage of women with breast cancer in the study sample was with 1 to 5 times of pregnancy and breastfeeding regularity (37.5%). The mother after giving birth needs to recover her body from the effects of pregnancy and also increase the number of pregnancies reduce the incidence of breast cancer because in this case hormones would be at a constant level in the normal activity (30). Except governing always ask for reducing the reproductive rate.

### Table 4-A: Sample distribution by number of pregnancies

<table>
<thead>
<tr>
<th>No. of pregnant times</th>
<th>No. of patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>non</td>
<td>7</td>
<td>21.9%</td>
</tr>
<tr>
<td>1 to 5</td>
<td>12</td>
<td>37.5%</td>
</tr>
<tr>
<td>6 to 10</td>
<td>8</td>
<td>25%</td>
</tr>
<tr>
<td>10 to 15</td>
<td>5</td>
<td>15.6%</td>
</tr>
<tr>
<td>total</td>
<td>32</td>
<td>100%</td>
</tr>
</tbody>
</table>

Fig. (4-A) sample distribution by number of pregnancies
Age of married and bearing the first baby:

The older age of marriage and bearing the first have a great effectiveness in causing breast cancer. Both events at age 30 or older increase the risk up to 7.0 times relative to when both events occurred younger than age 20. Whereas, the corresponding risk was 1.4 times when age between 20-30 years. These results were agreement with the previously reported result (31).

Table 5-A: Age of married and bearing the first baby.

<table>
<thead>
<tr>
<th>Age of married</th>
<th>No.</th>
<th>%</th>
<th>Age of bearing the first baby:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 years</td>
<td>3</td>
<td>9.87</td>
<td>4</td>
</tr>
<tr>
<td>20-30 years</td>
<td>8</td>
<td>23.29</td>
<td>3</td>
</tr>
<tr>
<td>&gt;30 years</td>
<td>21</td>
<td>66.84</td>
<td>25</td>
</tr>
</tbody>
</table>

![Graph showing age of married and bearing the first baby](image)

**Fig. (5-A) Age of married and bearing the first baby**

B- The way of discovering the disease and the risk factors increase the prevalence of breast cancer

Sample distribution by risk factors

Table 1-B: Risk factors in breast cancer from the perspective of patients

<table>
<thead>
<tr>
<th>cause</th>
<th>percent</th>
<th>number of patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.6</td>
<td>13</td>
</tr>
<tr>
<td>hereditary</td>
<td>15.6</td>
<td>6</td>
</tr>
<tr>
<td>Cigarettesmoking</td>
<td>3.13</td>
<td>1</td>
</tr>
<tr>
<td>Changes in hormone levels</td>
<td>9.38</td>
<td>3</td>
</tr>
<tr>
<td>Toxic chemicals</td>
<td>9.38</td>
<td>3</td>
</tr>
<tr>
<td>radiation</td>
<td>6.25</td>
<td>2</td>
</tr>
<tr>
<td>diet/obesity</td>
<td>12.5</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>32</td>
</tr>
</tbody>
</table>
We found in our questionnaire table (1-B); the risk of breast cancer increase by ageing (40.6%), the hereditary factors develop risk by (15.6%). It was reported that a family history of breast cancer had little effect on the risk in women with non-proliferative lesions. However, the risk in women with atypical and a family history of breast cancer was eleven times that in women who had non-proliferative lesions without a family history.

The change in hormone levels and the toxic chemicals increase risk by 9.38% only. Statistical analysis shows no significant difference between the results of both risks (p > 0.05). While the changing in lifestyle considered a second cause of disease (12.5%). The increase of the body fatness increases the risk of breast cancer. The World Cancer Research found that evidence increase the relative risk of postmenopausal breast cancer. Because adipose-associated with the obesity increases the conversion of androgens to estrogen, mammary adipose tissue thought to be an important source of local estrogen production. Estrogen is a potent mutagen for mammary cells, has long been implicated in the development of mammary tumors. Statistical analysis shows a clear significant difference (p > 0.05).

1- personal history of breast cancer

Table 2-B: Recurrence of breast cancer.

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>percent</th>
<th>Patient no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>40.6</td>
<td>13</td>
</tr>
<tr>
<td>No</td>
<td>59.4</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>32</td>
</tr>
</tbody>
</table>

Table (2-B) and figure (2-B) shows that the patient with a new cases of breast cancer is 59.4%; That means the lack of awareness of the breast cancer or increase the probability of the disease. The increment of the risk factor maybe one of the main causes. The increase in awareness of breast cancer risks and detection is necessary.

Fig. (1-B) Sample distribution by risk factors.
Time of Menstruation:
The early age of menstruation was one of the main causes of the breast cancer disease. As shown in table 4, patients who have menstruation before age 12 have a higher risk to get breast cancer.\(^{(36)}\)

Table 3-B: Menstruation time.

<table>
<thead>
<tr>
<th>Menstruation</th>
<th>Percent %</th>
<th>PatientNo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>before age 12</td>
<td>56.25 %</td>
<td>18</td>
</tr>
<tr>
<td>after age 12</td>
<td>43.75 %</td>
<td>14</td>
</tr>
<tr>
<td>total</td>
<td>100%</td>
<td>32</td>
</tr>
</tbody>
</table>

Menopause time:
As shown in table (4-B), patients who have menopause after age 50 have a higher risk to get breast cancer. By asking those women most of them take a hormonal replacement therapy. Importantly, breast cancer risk elevations appear to be higher among women who initiate treatment at the menopause, compared to women who do not have a menopausal treatment.\(^{(37)}\) Menopausal hormone was a combination of reproductive hormones; estrogen and progesterin hormones. Reproductive hormones are thought to influence breast cancer risk by increasing cell proliferation, thereby increasing the likelihood of DNA damage, as well as promotion of cancer growth. Women should consider the increased risk of breast cancer associated with the use of estrogen and progesterin when evaluating treatment options for menopausal symptoms.

Table 4-B: Menopause time

<table>
<thead>
<tr>
<th>Menopause time</th>
<th>Percent %</th>
<th>PatientNo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>before age 50</td>
<td>40.6%</td>
<td>13</td>
</tr>
<tr>
<td>after age 50</td>
<td>59.4%</td>
<td>19</td>
</tr>
<tr>
<td>total</td>
<td>100%</td>
<td>32</td>
</tr>
</tbody>
</table>

Discovery of the disease:
Table (5-B) shows that most common way of discovering the disease. The highest percentage of patients discover the disease by self-examination tests (46.9%). This indicates increasing the patients’ awareness which is a great importance in breast cancer screening. It also increases the healing rate.\(^{(38)}\)

Table 5-B: Discovery of the disease

<table>
<thead>
<tr>
<th>discover the disease</th>
<th>number of</th>
<th>percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance</td>
<td>9</td>
<td>28.1</td>
</tr>
<tr>
<td>Self-examination</td>
<td>15</td>
<td>46.9</td>
</tr>
<tr>
<td>Another reason</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>total</td>
<td>32</td>
<td>100%</td>
</tr>
</tbody>
</table>
The role of nanotechnology in the treatments: -
Sample distribution by kind of therapy.

**Table 1-C:** Sample distribution by kind of therapy

<table>
<thead>
<tr>
<th>kind of therapy</th>
<th>Percent %</th>
<th>Patient No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>chemotherapy</td>
<td>31.25%</td>
<td>10</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>50%</td>
<td>16</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>9.38%</td>
<td>3</td>
</tr>
<tr>
<td>surgery</td>
<td>9.3%</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100%</strong></td>
<td><strong>32</strong></td>
</tr>
</tbody>
</table>

Fifty percent of patients have a targeted therapy which indicates the importance of nanotechnology in breast cancer therapy (Table 1-C). As malignancy has become a serious threat to human health, and morbidity and mortality rates have been rising in recent years. Recent studies challenge and interesting is to develop effective therapy for cancer.

**Sample distribution of the usage of Epirubicin and its influence in therapy.** Although the percentage of patients using Epirubicin (43.75%) is less than those who do not use it (56.25%) as shown in Table 2-C, Table (3-C) but patients who influence a good effectiveness from Epirubicin HCl is 78.6%. The patients who have inappropriate therapy with Epirubicin HCl are only 21.4%.

**Table 2-C:** Sample distribution by use of Epirubicin.

<table>
<thead>
<tr>
<th>Use Epirubicin</th>
<th>Patient No.</th>
<th>Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>14</td>
<td>43.75</td>
</tr>
<tr>
<td>no</td>
<td>18</td>
<td>56.25</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
The duration of using Epirubicin to give an effective therapy inpatients:-
The influence and effectiveness of the medication starts within 3 months of starting treatment, some patients need only to 3 months to show the therapeutic effect of the medication they are 18.2% but the most patients show the therapeutic effect of the drug in 9 months 54.5% as table (4-C) shows. The results were agreement with the previously reported by Baldini E. 2002, etal who found that using Epirubicin in breast cancer therapy especially in combination with cyclophosphamide reduces the duration of therapy up to 6 months (41).

**Table 4-C:** Time that Epirubicin takes to give effect of in patients.

<table>
<thead>
<tr>
<th>Effective of therapy in/month</th>
<th>Number of patients</th>
<th>Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 months</td>
<td>2</td>
<td>18.2%</td>
</tr>
<tr>
<td>9 months</td>
<td>3</td>
<td>27.3%</td>
</tr>
<tr>
<td>14 months</td>
<td>6</td>
<td>54.5%</td>
</tr>
<tr>
<td>total</td>
<td>11</td>
<td>100%</td>
</tr>
</tbody>
</table>

Side effect of Epirubicin:-
Epirubicin HCl depends in its nanoparticles form to targeting the cancerous cells so it’s not effecting on normal cells; that’s why the side effects present by 18.2% as a serious while a 81.8% is common side effects.
Generally chemotherapy targets cell whether normal or cancerous cells; which leads to harm the healthy cells which have a high rate of growth and multiplication include cells of the bone marrow. However; the reducing of the serious side effect and duration and the highly effectiveness of the drug can be related to its nonstructural. Using multiwall carbon nanotubes (MWCNTs) in Epirubicin drug which depend on adsorption ionization methods antineoplastic agent help to be one of the most available drugs in treating breast cancer efficiently and effectively. It allows the medication to transport and target the drug to be effective Nano-carriers for anti-tumor therapies.

Epirubicin has a favorable safety profile and less side effects after short duration of the treatment. Several studies were done to identify the expanding role of Epirubicin in the treatment of breast cancer. These studies were matched with our study in the following point: first, Epirubicin has advancement in breast cancer treatment. After studying its effect across a range of subgroups of women with breast cancer including premenopausal and postmenopausal women, women with axillary lymph node-positive and negative tumors, and women with either hormone receptor-positive or negative tumors of Epirubicin have been observed.

As previously reported, it is being equally effective and better tolerated than Doxorubicin in women with metastatic breast cancer and has generally improved relapse-free and overall survival compared with standard adjuvant therapies, including CMF.

Trials of Epirubicin-based regimens in the adjuvant setting are ongoing, and combinations with newer cytotoxic agents such as the Taxanes, Trastuzumab, and Bisphosphonates are also being explored in an effort to continue to improve outcomes for patients with breast cancer.

Epirubicin also has potential advantages in increasing rate on breast-conserving surgery especially in combination with Paclitaxel. They enable lumpectomy in a substantial proportion of women who were previously deemed to not be suitable candidates for breast-conserving surgery.

Epirubicin is favorable in the case of the risk of developing congestive heart failure is low.

Epirubicin is active in metastatic breast cancer patients who have previously received Anthracyclines treatment in the adjuvant setting, in advanced breast cancer, and has marker efficiency of Epirubicin in primary breast cancer therapy.
It improves disease-free and overall survival in node-positive breast cancer patients\(^{(48)}\) and it is extensively and rapidly metabolized by the liver and also metabolized by other organs and cells, including red blood cells. Epirubicin and its major metabolites are eliminated through biliary excretion and, to a lesser extent, by urinary excretion. The results indicated the reduced accumulation in the body which lead to reducing the serious side effect.

**The study end point:**

**Primary endpoint:**
The effectiveness of the drug in the therapy was more than other chemotherapy. The drug rates were significantly higher with low duration.

**Secondary endpoint:**
- Reducing the most common side effect occurs with all other chemotherapies.
- Frequencies of the patient hospital income were decreased because of fast progression in patient health in less duration.
- Effective of the therapy was highly observed with patients treated with Epirubicin HCl drug

**Conclusion:**
The present study aimed to assess the prevalence of breast cancer in Taif city, the risk factors cause the disease and the effectiveness of Epirubicin HCl drug in the treatment as an example of nanosystems drug by screening 300 women. From all the previous results we concluded that:

- More than 10% of the patients have breast cancer in a period about 15 months indicating the highest probability of breast cancer diseases. Breast cancer considered one of the most important causes of death in women.
- Risk of breast cancer disease increased by aging; Since the samples of the study were taken for patients in 21 ages and above 70 years and by comparing between patients in their age; we found that the risk of breast cancer increased by aging 40.6% as present in the study and highly distributed at the ages between 41 to 50 years old.
- The personal history of breast cancer increased the risk to develop a new lesion or recurrence to the first one, we record in this study a 46.9% patient has recurrent disease
- Breast cancer is the most prevalent among married women; we found in our distributed questionnaire the prevalence of breast cancer disease in married woman (68.8%).
- The lack of movement is one of the contributing factors and important to develop breast cancer; therefore housewives developed the highest risk of breast cancer 43.7%, and this risk decreased if she takes a walk at least for one hour in outdoors like student or employed who show the least distributed by 18.7 and 37.5% respectively.
- Increased number of birth will reduce the risk of breast cancer; especially among women have 1 to 5 times of pregnancy and breastfeeding regularity (37.5%).
- If there is a family member having breast cancer this will increase the risk; especially if he is a very close family member like a mother or sister.
- A longer lifetime exposure to the hormones estrogen and progesterone as hormonal supplement therapy increases the risk of breast cancer. In this study, results appear in patients who started menstruating before age 12 by and those who continued through after 50 years old or who was using supplement hormonal therapy.
- Environmental chemical compounds found around us in certain cosmetics, personal care products and pesticides has low effect in increasing the risk of breast cancer.
- High-fat diets can lead to being overweight or obese, which is a breast cancer risk factor
- The patients who exposed to radiation because nature of their work enhanced risk of getting breast cancer, they are presented in this study by 6.25%.
- Cigarette smoking cause many cancer types one of it causing breast cancer in smoked patients or exposed to smoke, a 3.13% from patients in this study have breast cancer due to smoking even though the lower percent.
- The high awareness of breast cancer and how to discover the disease, improve the early detection of the disease and enhance recovery chances. In this study, 46.9% of patients discover the disease by self-examination.
- Highly awareness from doctors of using targeted drug in breast cancer therapy is very effective in managing the disease. In our study we found the targeted drug of 50% patients set targeted drug in their therapy.
Epirubicin is a special type of chemotherapy due to its dependence on nanoparticles in its composition, so it's preferred by doctors and patients in its use. This what we demonstrated in this study; the percentage of patients who are using Epirubicin in their therapy is 43.75%.

The effectiveness of Epirubicin being between 3-9 months. As 54.5% of patients have the therapeutic effect of the drug in 9 months.

Epirubicin is a targeted cancer therapy; its effectiveness is between 3-9 months. 54.5% of patients have the therapeutic effect of the drug in 9 months.

Epirubicin as a targeted cancer therapy has less toxicity than traditional chemotherapy drugs because it targets cancer cells more than normal cells. However, targeted cancer therapies can have substantial side effects, but because it contains nanoparticles form targeting the cancerous cells, we found that 81.8% of patients have common side effects, while 18.2% was a serious side effect.

Epirubicin is an Anthracyclines drug using Nanoparticle in the therapy which represents advancement in breast cancer treatment. In addition, it is being equally effective and better tolerated than other chemotherapy, due to its depend in its nanoparticles form to targeting the cancerous cells. This explains why it has the highest efficacy and the lowest side effects than other chemotherapy agents.

Recommendation:-

- Spread awareness about breast cancer detection, and how it's important to discover the disease and increase the effectiveness of therapy if the disease is detected early.
- Work on the preparation of educational programs by radio, television, social media and other media on the risk factors that cause breast cancer so that people can prevent this disease early.
- Encourage mothers to continue breastfeeding their children even after providing additional food because breastfeeding reduces the incidence of breast cancer.
- The role of health and media organizations around the initial actions of infected women and about how note and examine any abnormal swelling through health education for the family.
- Encourage doing exercises or at least a walk in outdoors for one hour daily because exercises and fresh air reduces the risk of getting breast cancer.
- Continuous checkup and self-examination for women having high risk to get breast cancer, e.g., family or personal history of breast cancer.
- Stay away from taking hormonal medications and contraception without consulting your doctors.
- Check up the environmental chemical and make sure it's not carcinogenic factors especially in work area.
- Balancing foods and diet intake, to regulate the exercise and reducing the chances of getting breast cancer.
- Protect people who work in the fields of radiation by:
  - Distance: the radiation intensity decreases as we move away from the source, and this means we should keep a suitable distance away from the radiation source.
  - Time: it's commensurate with the dose of radiation directly proportional to the exposure time, must perform work in the region where the radiation intensity is as soon as possible and efficiently.
- Armor: The armor is a protective barrier placed around the radioactive source or a source of radiation device.
- Increase the awareness of doctors, health care providers, and patients about the role of medications that contain nanotechnology in its composition, e.g., Epirubicin drug and how it reduces the side effects and increase the effectiveness of the therapy.
- We should use a suitable simple and safe nanosystem preparation technique, method of preparation, and the polymer among the various possible methods to produce nanoparticles with desired size range with targeting effect and depending on the physicochemical characteristics of the drug.
- Using of Epirubicin in treatment of breast cancer therapy for 3-9 months is recommended.

Summary:-

This study has been done to assess the prevalence of breast cancer in Taif city and the role of Nanotechnology in Epirubicin drug in its therapy. We conducted this study period from 21 Sep. 2014 to 25 Dec. 2015 by taking samples from patients presented to the hospital in 2014 only. By screening 300 women in Taif, we presented to the hospital in 2014, then followed up the cases to Dec. 2015 and analyzed the results statistically using SPSS to achieve the objectives of the research. We found that the patients who have breast cancer is 10.7% in 32 cases. The highest percentage of women with breast cancer is in the age group (41-50). Married women are more susceptible to breast cancer than single women (68.8%). Supreme percentage of women with breast cancer in the sample is housewives and the lowest percentage is students. Risk of breast cancer increase by ageing, family history and changing the hormone levels High.
awareness of breast cancer screening allowed to 46.9% of patients examine themselves and helped them to discover the disease. Reducing the pregnancy age, marriage age and pregnancy numbers (1 to 5) and breastfeeding help in reducing the probability of breast cancer disease. Nanotechnology has great importance. Nanoparticles presented in the Epirubicin HCl shows high effectiveness and less side effects in a period between 3-9 months due to targeting the cancerous cells.

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Abbreviations:-
1. BC : Breast cancer
2. CNT : carbon nanotubes
3. DCI : Ductal carcinoma in situ
4. DLT : dose-limiting toxicities
5. DNA : Deoxyribonucleic acid
6. EPI : Epirubicin hydrochloride
7. f-CNTs : functionalized carbon nanotubes.
8. GRAS : generally recognized as safe
10. IV : intravenous
11. LUVs : large unilamellar vesicles
12. MLVs : Multilamellar vesicles
13. MSNs : mesoporous silica nanoparticles
14. MTD : maximum-tolerated dose
15. MWCNTs : multi wall carbon nanotubes.
16. NNI : National Nanotechnology Initiative
17. PCL : polycaprolactone
18. pCR : pathologic complete response
19. PEG : polyethylene glycol
20. PEI-PEG : polyethyleneimine-polyethylene glycol
21. PFS : progression-free survival
22. PLA : poly lactic acid.
23. Ppy : polypyrrole
24. RNA : Ribonucleic acid.
25. SLN : Solid lipid nanoparticles
26. SUVs : small unilamellar vesicles
27. SWCNT : single wall carbon nanotubes.