Review

TREATMENT OF BREAST CANCER: A BRIEF REVIEW

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ABSTRACT: Breast cancer is one of the leading causes of death in women all over the world. It is equally common in under developed and developed countries. Incidence of breast cancer is increasing at young age due to environmental and genetic factors. For the treatment of early and late stages of breast cancer, different cancer chemotherapeutic agents are used alone and in combination. Although these drugs treat effectively breast carcinoma but they can also exert their mutagenic and cytotoxic effects in certain cases. In this study we have documented the chemotherapeutic agents used in breast cancer.

KEY WORDS: Breast Cancer, Environmental Factor, Genetic Factor

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Introduction:

As far as cell proliferation and differentiation is concerned, some body cells do not undergo normal division. A specific term is used for these cells called cancer as they undergo uncontrolled division. [1][29]. Different types of mutations have been described in literature. Deletion, modification or insertion of a single base pair is called as point mutation. While chromosomal mutations can result as a rearrangement of DNA and large deletions due to chromosomal breaks or loss or gain of complete chromosome. Very sophisticated techniques are available to determine the chromosomal damage in mammalian cells. Magnified chromosomal images are used to find these molecular changes in DNA. While for detection of gene mutations in bacteria relatively simpler techniques are available [2].

Addition of Taxane in estrogen receptor positive:

Females with estrogen receptor positive type of CA breast pathologically showed improved response (pCR) when Taxane was added and were given prolonged chemotherapies pre-operatively as compared to three or four cycles of combination chemotherapy with FAC(5-FU, doxorubicin, cyclophosphamide). [3]. (Mazouni et al., 2007)

Treatment with Anthracycline:

Either early or advanced stage, treatment of breast cancer may include anthracyclines as an important component. Use of Anthracyclines is associated with cardio-toxicity. Patients with HER2 type CA breast who were previously treated with adjuvant AnthracyclineTrastuzumab regimen were facing high risk of cardiac toxicity. Pegylated liposomal doxorubicin, as a monotherapy as well as in combination with trastuzumab was equally active, but showed lower risk of cardiac problems as compared to conventional doxorubicin. Thus, for treatment of metastatic breast cancer, pegylated doxorubicin can be effectively administered with anthracycline . As a maintannace therapy, pegylatedDoxorubicin delayed tumor progression. The study supported pegylatedDoxorubicin use in patients presenting with MBC(metastatic breast cancer). [4]. (Verma et al., 2008)

Combination chemotherapy therapy:

Combination chemotherapy therapy is routinely used for the treatment of metastatic CA breast. Along with efficacy drugs also show their side effects. For maximum efficacy and minimum side effects , close monitoring of side effects is required. This is necessary to improve quality of life of the patient. Non cytotoxic newly developed chemotherapeutic drugs for treatment of metastatic CA breast are being considered. Ixabepilone/capecitabine and lapatinib/capecitabine were included in such combinations. Ixabepilone belongs to the class epothilones and is in clinical phase of drug development. Its mode of action is same as taxaned group. It by binding to the microtubules and inhibiting proliferation, inhibited DNA. It was active agtieainst tumor cells that were taxane-resistant. When given in combination with capecitabine ,MBC patient survival with taxane resistance was improved. Similarly, combination of lapatinib and capecitabine showed good activity against human epidermal growth factor-1 and 2 receptor. This increased the survival rate in MBC patients. Combination of paclitaxel and bevacizumab for MBC showed risk of toxicity and it is still under investigation [5].

Treatment with TAC:

For the treatment of breast cancer in advanced stage, TAC (Doxetaxel, Doxorubicin, Cyclophosphamide) was considered as a rescue chemotherapeutic regimen. A 56 years old metastatic breast cancer patient with heavy intraperitonial metastasis was treated with TAC in the hospital. Besides grade III neutropenia, no other significant side effect was observed in him, which was managed with G-CSF administration. After treating him with four cycles of TAC, his metastatic lesions ceased. This showed that TAC proved to be a rescue chemotherapeutic regimen for male patients with metastatic breast cancer [6].

Modern age of chemotherapy:

With advancements in targeted drug delivery on molecular levels, effectiveness of combination therapy is being increased and cellular cytotoxicity is being reduced with fewer side effects. This is the start of modern age of chemotherapy. Successful planning and proper selection of available treatment protocols can help in eradication of the disease. Moreover early stage treatment of breast cancer can improve the patient survival rate [7].

Treatment with Cyclophosphamide and doxorubicin:

A research was conducted to evaluate the use of alternative anticancer drug to treat docetaxel resistant MHRPC. Cyclophosphamide was for tested for this purpose as it is the commonly used drug for metastatic breast cancer. For this treatment, cyclophosphamide proved to be a successful treatment. For combined therapies like kinase inhibitors, immunotherapy and anti angiogenesis, it was shown to be the favoured drug [8]. .A study was conducted to elaborate the in vitro and in vivo antigenotoxic and mutagenic effects of knownanti tumor agents like cyclophosphamide and doxorubicin when used in combination with flavonoids and apigenins at different doses. The in vitro results showed lesser mutagenicity when doxorubicin and apigeninwas used in combination while cyclophosphamide showed no change in mutagenicity level. Micronucleus activity in relation to cyclophosphamide was decreases markedly in in vivo results of apigenic agents [9]. Doxorubicin and anthracyclines have known mycocarial side effects .These side effects are due to formation of oxidative stress and free radicals. A female with breast cancer was treated with liposomal infusion of doxorubicin. A s a result she developed acute myocardial infarction. This was confirmed by angiography that this infarction was a result of this chemotherapeutic drug therapy[10]. .Cytotoxicity of cyclophosphamide,doxetexal and paclitaxal was studied by using cell lines L929 and P388D1 by incubating them with cytochrome P450. Rat liver microsomesused were not cytotoxic. When CYP was incubated with CYP3A-, CYP2E1-, and CYP2P1-induced microsomes for 2 hours, cytotoxic products were produced. In P388D1cell lines , cytotoxicity of DTX and PCT became apparent after 24 hours of 2 hours incubation period with drugs . Moreover, CYP2E1 microsomes enhanced their effects , while CYP3A induced microsomes decreased them. DTX and PCT showed dose related cytotoxicity in hella cell lines and in P388D1. .It was also shown that there is a role of enzymes in the ultimate effects of anticancer drugs . Due to difference in their mode of action DTX and PCT showed delayed cytotoxicity as compared to CYP [11].

Comparative study of doxorubicin, paclitaxel and FAC:

The efficacy of doxorubicin and paclitaxel and FAC (5-FU, doxorubicin, cyclophosphamide) was compared in an independent phase III randomized trial for MBC patients. Original case reports from oncologists and radiological images were taken from expert radiologists. Time to disease progression of the disease and survival rate were analyzed in this blinded clinical trial. As a result, in metastatic breast cancer patients, doxorubicin and paclitaxel were proved to be advantageous over FAC regimen as far as the above mentioned parameters were concerned [12].

Demography study of breast cancer:

A study was conducted to evaluate that which age group among females was more susceptible to breast cancer. Only 5% cases of breast cancer were registered who were under 40 years of age but it was found that at younger age the disease was quite more progressive. Cases of female breast cancer patients registered from 2005 to 2009 with mastectomy followed by reconstruction were collected. Data of total 671 patients was reviewed after selection. 16 % patients were under 40 years of age while 84 % patients were above 40. The results collected from the data showed that the group of patients under 40 was more prone to progressive breast cancer, receive radiation, undergo mastectomy, and show delayed reconstruction. The conclusion drawn was that radiation therapy in advanced tumor cases coupled with prophylactic contra lateral mastectomy can lead to breast reconstruction in females below 40 [13].

Vinorelbin and epirubicin

A study was conducted to compare effectiveness of vinorelbin and epirubicin with FEC (Flurouracil, epirubicin and cyclophosphamide) , a recsue regimen. The later combination proved to be successful for providing long term survival as for as treatment of MBC is concerned [14]. (Yan et al., 2010)

Paclitaxel and Carboplatin:

PC (Paclitaxel and Carboplatin) and FAC (5-FU, doxorubicin and cyclo-phosphamide) were given for treatment of patients with advanced stage breast cancer. They were given two different types of chemotherapy regimens i.e. Out of 25 patients, 9 patients (37%) were treated with PC regimen while 16 of them (66%) received FAC regimen. In 8% of the patients, minor response (MR) was seen, 16% patients showed partial response (PR) and 54% patients showed complete response (CR). Although FAC chemotherapy regimen did not resulted in any death but it was associated with more cardiac problems, vomiting, mucositis and alopecia. Thus it was concluded that PC combination was better tolerated. It reduced disease recurrence and improved survival rate as well[15]. (Akhtar et al., 2010)

Bevacizumab:

Bevacizumab has been used for the MBC patients as an additive drug with standard 1st line chemotherapy. The studies showed that bevacizumab treats MBC with better survival rate and lesser toxicity [16]. (Bravencova et al., 2010)

Breast cancer during pregnancy:

It was observed that there are chances of breast cancer to be diagnosed in pregnant women if they are the cases of late childbearing. However, such cases can be treated during 2nd and 3rd trimester with FAC(5-FU,doxorubicin,cyclophosphamide). This treatment showed no significant problems and complications in the children that were exposed to this chemotherapeutic regimen during pregnancy in the uterus. But it was stressed that long term follow up of such children must be done in order to evaluate these cases for late adverse effects such as cardiac problems and infertility [17]. (Hahn et al., 2006)

Treatment with *Mitragynaspeciosa Korth*:

Mitragynaspeciosa Korth was used as a traditional plant to elevate energy level in fever, illness or diarrhea. Antimutagenic and mutagenic response of this plant was checked by Ames *Salmonella triphimurium* assay. These activities were checked against TA 100 and TA 98 strains with and without metabolic activation. S-9 was used activate metabolic system. Negative control plates were used to evaluate the mutagenicity considering 2 fold increase in colonies as cut off value. As far as the mutagenic properties were concerned no mutagenicity was found in test extract in both strains with and without S-9. But significant and strong antimutagenic properties were found in twoconcentrations of the plant with and without metabolic activation system [18]. **(**Ghazali A R et al, 2011)

Disorder with anti-cancer drugs:

Potential health hazards of anticancer drugs were studied and found that anticancer drugs may be mutagenic , carcinogenic or teratogenic. Chemotherapy may lead to secondry malignancies. Urine of the nurses formulating and handling chemotherapeutic agents as showed both positive and negative results for urinary mutagenicity for different chemotherapeutic agents. Occupational handling with anticancer agents can cause pregnancy disorders, spontaneous abortion or other malfunctions [19]. .Different effects of anticancer drugs were studied using mouse testes cells. Difffernt doses of various chemotherapeutic drugs were given to male mice as single injections . Prednisone and 6-mercaptopurine showed very little cytotoxicity. Methotrexate, *cis*-platinum, and mechlorethamine and cyclo-hexylchlorethylnitrosourea did not killed the stem celss significantly. Bischlorethyl nitrosourea, ,mitomycin C, actinomycin D, chlorambucil, 5-fluorouracil and procarbazine killed some stem cells. 5 FU and cisplatinum caused spermatocyte killing while cisplatimun showed spermatids killing. These were the results after a single injections of chemotherapeutic drugs on the testes of mice. So in humans, it was not predictive that which drug can result in long term azoospermia [20].

Topomeraseisomerase inhibitor anticancer agents donot interact with DNA covalently even then they can be mutagenic causing changes at chromosome level rather than gene level. Topoisomerase inhibitors cause changes in replication fork. In case of treatment with topoisomerase enzyme inhibitors programmed cell death may be an alternative pathway of mutagenesis [21].

There is a correlation between mutagenicity and carcinogenicity in cancer chemotherapeutic agents. Adriamycin, daunomycin, hycanthone, chlornaphazin, ,nitrogen mustard, uracil mustard, cyclophosphamide, isophosphamide, melphalan,

thio-tepa and 1-propanol-3,3′-iminodimethanesulfonate showed positive results for carcinogenicity. Although Actinomycin D and bleomycin were carcinogenic but they showed non-mutagenic results .While methotaxate which was noncarcinogen, showed negative result in this study.Tilorone and 6-mercaptopurine, which were noncarcinogens, showed mutagenic results in this study[22].

Mutagenicities of cyclophosphamide, 6-mercaptopurine, daunomycin hydrochloride, Adriamycin hydrochloride, mitomycin C, and were confirmed in a study byusing*Salmonellatyphimurium* TA92,TA98 and TA 100. For the very first time, four agents namely busulfan, pipobroman , 1-(4-amino-2-methylpyrimidine-5-yl)methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride and carbazilquinon were shown to be mutagenic [23].

Doxorubicin and Daunorubicin derivatives studied with *E. coli, Salmonella typhimurium* and in V79 Chinese hamster cells were proved to be cytotoxic as well mutagenic in prokaryotic and eukaryotic cells. The derivates like 4-desmethoxy- and 4'-desoxy-derivatives showed more activity than their parent compounds. This showed that in biological properties, noticeable changes occur in anthracycline antibiotics with changes in aglycone and sugar moiety. This in vitro activity can be corelated with in vivo tumor potency [24].

Mutagenicity is associated with most of the topoisomerase I and topoisomerase II inhibitors. Various anticancer drugs has anti topo II enzyme activity. But only some anticancer drugs show anti topo I enzyme activity which are used clinicaly. Although they do not covalently bind with DNA even then they show mutagenic properties. They show effects on chromosome level rather than gene [25].

In head and neck cancer patients, anticancer immunity is increased by cisplatin and 5-FU by cytokine and killer cell induction. This showed that some anticancer drugs can stimulate anticancer immunity [26].

E. latissima and Kigelia Africana:

Seven different Sudanese traditional medicine species were extracted. Their antibacterial and anti-cholinesterase activity was studied after their screening. While their mutagenic potential were detected by the Ames test.Ethanolic extracts of roots and bark of of*E. latissima*and*Kigeliaafricana* showed the lowest IC50 value , 0.09 mg/ml. While the Ames test showed no mutagenicity in these plant extracts [27].

Toxicity profile of FAC and TAC:

In a study toxicity profile of FAC (5-FU, Doxorubicin, Cyclophosphamide) and TAC (Doxetaxel, Doxorubicin, Cyclophophamide) were compared in females with breast cancer. The study was done with and without prophylactic G-CSF(PPG). Neutropenic fever associated with TAC markedly decreased with PPG addition during chemotherapy. Patients, who were treated with FAC, enjoyed better quality of life as far as health is concerned. In the final cycle of chemotherapy, PPG addition improved treatment standard and better results were observed [28].

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