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Review Paper on Immunotherapy in Metastatic Cancer

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Abstract- ***Immunotherapy is a current medication approach in the field of cancer treatment. The main objective of this therapy is to boost patient' s own immune system to kill cancer cells. This therapy is known to have less side effects than conventional available therapies. In this review, different immunotherapeutic approaches are discussed in the context of metastatic breast cancer including monoclonal antibodies, cancer vaccines and immune checkpoint blockade systems. Here, different aspects of metastasis is discussed in details with respect to most prone organs for breast cancer metastasis This review includes present and available treatments of breast cancer and shows advantages of immunotherapy over chemotherapy and radiation therapy. It highlights different types of immunotherapy. The main objective of this study is to show the positive effects of immunotherapy on the patients of advanced breast cancer and to influence further research in this field.***

I. INTRODUCTION

Breast cancer is an abnormal condition of the body chiefly found in female individual where the cells of the mammary gland start to show uncontrolled proliferation. These cells show uncontrolled proliferation. This condition arrives due to some mutation in gene. This ultimately result in formation of lumps in the breast tissue. (https://ww5.komen.org/...Breast_Cancer)

There are two types of mammary gland carcinoma – (https://www.cancer.org/cancer/breast-cancer)

- Ductal carcinoma starts in the tubes (ducts) that carry milk from the breast to the nipple. This is the most prevalent form of breast cancer.
- Lobular carcinoma starts in the parts of the breast, called lobules, which produce milk.

Another division can be made on the basis of invasion:-

- Invasive breast cancer – It occurs when abnormal cells from inside the milk ducts or lobules break out into nearby breast tissue. Cancer cells can travel from the breast to other parts of the body through the blood stream or the immune system. They may travel early in the process when the tumor is small or later when the tumor is large.
- Non-invasive breast cancer – It describes a cancer that has not spread beyond the ducts or lobules where it began. Ductal carcinoma in situ (DCIS) is a type of non- invasive breast cancer. DCIS occurs when abnormal cells grow inside the milk ducts, but have not spread to nearby tissue or beyond. The term " in situ" means " in place." Although the abnormal cells have not spread to tissues outside the ducts, they can develop into invasive breast cancer.

Invasive breast cancer that spreads to other parts of the body is called metastatic breast cancer. These cancer cells can spread to other parts of the body, such as the liver, lungs,

bones and brain. The cancer cells again divide and grow out of control and form new tumors. Even though the new tumors are growing in another part of the body, the cells still show the properties of breast cancer.(https://www.cancer.gov/publications)

II. METASTASIS

Metastasis is a phenomenon in which cancer cells spread from its site of origin to another organ without being directly connected with it. The new secondary growth thus generated are referred to as metastases. It is also termed as metastatic cancer or stage 4 cancer. Thus, metastasis helps in cancer progression by spreading the disease from one organ to another organ.(Leber MF, 2009)

The characteristics of metastasis are (Britta Weigelt 2005)

- separation from the primary tumor
- invasion through tissues around the initial lesion and penetration of their basement membranes
- entry into the blood vessels and survival within blood - spread via blood vessels (hematogenous spread)

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- entry into lymphatics or peritoneal cavity - spread via lymph channels (lymphatic spread)
- reaching the distant organ like lungs, liver, brain, bone etc.
- formation of a new lesion along with new blood vessels feeding the tumor - formation of new blood vessels is termed angiogenesis
- cells undergo epithelial to mesenchymal transition (EMT). It is a process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties to become mesenchymal stem cells

Metastasis involves the following steps(Jun yokota 2000) -

- Cellular Heterogeneity and Proliferation - Primary tumour cells have highly potential and heterogenous cells who have the potentiality to invade the organs. They also have the ability to evade the growth suppressor and inhibit the regulation of cellular proliferation by cell cycle check point and DNA damage mechanisms.
- Epithelial to Mesenchymal transition (EMT)- This is the phenomenon where epithelial cells lose their polarity and cell-cell adhesion and transformed into mesenchymal cells.
- Interactions with tumor stroma - Progression in cancer requires activation of a number of cells in the adjacent stroma via paracrine signaling. Stromal cells, including endothelial cells, pericytes, fibroblasts, and leukocytes, consists of a number of protumorigenic factors which promotes tumor growth. The two prominent cell types are the cancer-associated fibroblasts (CAFs) and the pericytes
- Local Invasion - Phenotypically aggressive clone are produced and spread of the tumor consists of a series of two sequential steps: namely, invasion of the extracellular matrix (ECM), with penetration into the vasculature and hematogenous dissemination to the site of secondary tumor.
- Colonization - This process is mediated by organ specific infiltration followed by neoangiogenesis and proliferation.

III. CURRENT TREATMENTS AVAILABLE FOR METASTATIC BREAST CANCER

Drugs used for treating metastatic breast cancer are as follows (https://www.drugs.com and https://www.cancer.gov)

Sr. No.	Drug name	Side effects
1.	Femara (Chemical name: Letrozole)	pain in the legs, arms, or back, nausea, depression, headache, joint pain, weakened bones, fatigue, difficulty breathing
2.	Xeloda Chemical name: Capecitabine	diarrhea, nausea, vomiting, mouth and throat sores, loss of appetite or decreased appetite, excessive water loss from the body (dehydration), hand-foot syndrome, irregular periods --
		this can include temporary cessation
3.	Herceptin (chemical name: trastuzumab)	weakening of the heart muscle, low white blood cell count, diarrhea, anemia, abdominal pain
4.	Arimidex (chemical name: anastrozole)	weakness, fatigue, headache, mood swings, depression, nausea, mild diarrhea, increased or decreased appetite, sweating, hot flashes, vaginal dryness, temporary hair thinning, joint pain, bone pain and weakness, lower bone density
5.	Mitotaxtrone (brand name: Novantrone)	low white blood cell counts, nausea, vomiting, diarrhea, hair loss, constipation, heartburn, loss of appetite, mouth sores, nail changes, weakness, fatigue, headache, back pain, runny nose, irregular periods -- this can include temporary

		cessation
6.	Navelbine (chemical name: vinorelbine)	low white blood cell counts, numbness and tingling in the hands and feet (neuropathy), nausea, vomiting, hair loss, mouth sores, hair changes, diarrhea, irregular periods -- this can include temporary cessation
7.	Faslodex (chemical name: fulvestrant)	hot flashes, nausea, vomiting, diarrhea, constipation, stomach/abdominal pain, sore throat, back pain, headache, injection site pain
8.	Tamoxifen	hot flashes, irregular periods, vaginal discharge or bleeding, mood swings, depression, weight gain, blood clots
9.	Tykerb (chemical name: lapatinib)	diarrhea, rash, neuropathy (tingling in the hands and feet), nausea, vomiting, fatigue, loss of appetite, mouth or throat sores, insomnia, liver problem
10.	Ibrance (chemical name: palbociclib)	anemia (low red blood cell count), fatigue, nausea, neuropathy, mouth sores, hair thinning or loss, diarrhea, vomiting, weakness, decreased appetite, neutropenia (low white blood cell count), infections, blood clots
11.	Taxol (chemical name: paclitaxel)	low white blood cell count, susceptibility to infection, allergic reactions, hair loss, numbness in the fingers and toes (neuropathy), weakness, vomiting, diarrhea, mouth sores, irregular periods -- this can include temporary cessation
12.	Taxotere (chemical name: docetaxel)	low white blood cell count, susceptibility to infection, fluid retention, allergic reactions, hair loss, numbness in the fingers and toes (neuropathy), nausea., vomiting, constipation, taste changes, fatigue,muscle pain, bone or joint pain, nail changes, mouth or throat sores watery eyes, irregular periods -- this can include temporary cessation
13.	Abraxane (chemical name: albumin-bound or nab-paclitaxel)	low white blood cell count, anemia (low red blood cell count), infections, swelling (edema), nausea, vomiting diarrhea, neuropathy (nerve damage), muscle or joint pain
14.	Capecitabine	fatigue, low white blood cell count, anemia (low red blood cell count), nausea, hair thinning, diarrhea, irregular periods -- this can include temporary cessation
15.	Gemzar (chemical name: gemcitabine)	fatigue, low white blood cell count, anemia (low red blood cell count), nausea, hair thinning, diarrhea, irregular periods -- this can include temporary cessation
16.	Halaven (chemical name: eribulin)	low white blood cell count, anemia (low red blood cell count),fatigue weakness, hair loss, neuropathy (numbness/tingling in the hands and feet) nausea, fever, constipation, irregular periods -- this can include temporary cessation.
17.	Perjeta (chemical name: pertuzumab)	birth defects, diarrhea, hair loss, low white blood cell count (neutropenia), nausea, fatigue rash, peripheral neuropathy (numbness, tingling, or burning in the hands and feet)

18.	Ixempra (chemical name: ixabepilone)	headache, hair loss, skin sensitivity skin, discoloration, nail changes, hand-foot syndrome, mouth or throat sores, taste changes, watery eyes, loss of appetite,weight loss, heartburn nausea vomiting, diarrhea, constipation, abdominal pain, bone or joint pain, muscle pain, memory loss, insomnia, weakness, fatigue, irregular periods -- this can include temporary cessation
19.	Adriamycin (chemical name: doxorubicin)	low white blood cell count, increased risk of bleeding from low platelet count, appetite changes, nail changes, hair loss nausea, vomiting, mouth sores heart problems, hand-foot syndrome, irregular periods -- this can include temporary cessation
20.	Afinitor (chemical name: everolimus)	lung problems, breathing problems, kidney failure, mouth sores, infections,rash, fatigue, diarrhea, decreased appetite
21.	Aranasp (chemical name: darbepoetin alfa)	blood clots, tumor growth/recurrence, heart problems, stroke, headache, vomiting, abdominal pain, diarrhea, constipation, joint pain, muscle pain, injection site pain
22.	Aredia (chemical name: pamidronate)	fever, fatigue, nausea, vomiting, bone pain at the start of treatment,loss of appetite, anemia, osteonecrosis of the jaw (loss of bone in the jaw)
23.	Fareston (chemical name: toremifene)	hot flashes, nausea, weight gain, allergic reactions (such as skin rashes), headache,
24.	Aromasin (chemical name: exemestane)	hot flashes, mood swings, depression, nausea, fatigue, increased sweating, increased appetite, weakened bones
25.	Avastin (chemical name: bevacizumab)	nosebleeds, high blood pressure, proteinuria (too much protein in the urine, a possible sign of kidney malfunction), fatigue, low white blood cell count, diarrhea
26.	Daunorubicin (brand names: Cerubidine, DaunoXome)	nausea, vomiting, loss of appetite, stomach pain, diarrhea, difficulty swallowing, hair changes, skin sensitivity, rash, nail changes, irregular periods -- this can include temporary cessation
27.	Doxil chemical name: doxorubicin)	low white blood cell count, increased risk of bleeding from low platelet counts, hand-foot syndrome, loss of appetite, nail changes, hair loss, nausea, vomiting, mouth sores, irregular periods -- this can include temporary cessation
28.	Ellence (chemical name: epirubicin)	nausea, vomiting, diarrhea, mouth sores, hair loss, low white blood cell count, irregular periods -- this can include temporary cessation
29.	Epogen (chemical name: epoetin alfa)	blood clots, tumor growth/recurrence, heart problems, stroke, headache, joint pain, muscle pain, nausea, vomiting, stomach pain, sleeping problems, diarrhea, constipation ,rash, itching, neuropathy
30.	Evista (chemical name: epoetin alfa)	hot flashes irregular periods vaginal discharge or bleeding mood swings depression trouble sleeping weight gain joint pain blood clots
31.	Flurouracil Brand name: Adrucil	diarrhea nausea vomiting loss of appetite vision or eye problems taste changes, metallic taste in mouth during infusion low white blood cell count irregular periods -- this can include temporary cessation

32.	Halotestin (chemical name: fluoxymesterone)	headache facial hair growth nausea acne anxiety insomnia
33.	Kadcyla (chemical name: T-DM1 or ado- trastuzumab emtansine)	anemia (low red blood cell count) fatigue nausea neuropathy mouth sores hair thinning or loss diarrhea vomiting weakness decreased appetite neutropenia (low white blood cell count) infections blood clots
34.	Kisqali (chemical name: ribociclib, formerly called LEE011)	nausea fatigue diarrhea vomiting headache back pain low white blood cell counts constipation heart problems known as QT prolongation liver problems
35.	Lupron (chemical name:	hot flashes mood swings loss of libido osteoporosis
	leuprolide)	
36.	Megace (chemical name: megestrol	loss of libido vaginal bleeding insomnia gas rash
37.	Methotrexate brand names: Amethopterin, Mexate, Folex	nausea vomiting joint pain diarrhea swelling in the feet and legs mouth sores hair changes rash irregular periods -- this can include temporary cessation
38.	Mitomycin (chemical name: mutamycin)	low white blood cell counts susceptibility to infection fatigue nausea vomiting hair loss mouth sores irregular periods -- this can include temporary cessation
39.	Neulasta (chemical name: pegfilgrastim)	bone and joint pain muscle pain spleen rupture pain in the upper left part of the stomach or tip of the left shoulder fever trouble breathing rash itching headache weakness constipation
		vomiting swelling
40.	Neupogen (chemical name: filgrastim)	bone and joint pain muscle pain headache nosebleeds spleen rupture pain in the upper left part of the stomach or tip o the left shoulder fever trouble breathing rash itching
41.	Thiotepa (brand name: Thioplex	low white blood cell count nausea vomiting loss of appetite fatigue hair changes irregular periods -- this can include temporary cessation
42.	Trelstar (chemical name: triptorelin)	hot flashes mood swings loss of libido osteoporosis
43.	Vincristin	diarrhea rash neuropathy (tingling in the hands and feet) nausea vomiting fatigue loss of appetite mouth or throa sores insomnia liver problems
44.	Xgeva (chemical name: denosumab	nausea vomiting diarrhea constipation hair changes numbness and tingling in the hands and feet (neuropathy) fatigue muscle aches muscle and abdominal cramps irregular periods -- this can include temporary cessation
45.	Zarxio (chemical name: filgrastim-sndz)	diarrhea nausea vomiting mouth and throat sores loss of appetite or decreased appetite excessive water loss from the body (dehydration) hand-foot syndrome irregular periods -- this can include temporary cessation
46.	Zoladex (chemical name: goserelin)	mood swings hot flashes loss of libido vaginal drynessbreast swelling or tenderness weight gain headaches bone pain

47.	Zometa (chemical name: zoledronic acid)	bone pain nausea vomiting fever fatigue constipation diarrhea loss of appetite teary eyes heartburn mouth sores depression vaginal discharge hand-foot syndrome hair changes osteonecrosis of the jaw (loss of bone in the jaw)

IV. CANCER IMMUNOTHERAPY

The immune system helps in regulating the growth of tumors. Inflammatory responses sometimes promote tumor growth, but it has been seen that some specific tumor adaptive immune response can effectively control tumor growth. Cancer cells progressively devise mechanisms to evade the body' s immune system. Cancer immunotherapy involves reactivation of the body' s adaptive immune response which is specific and have long- term memory in order to get rid of cancer. Thus, cancer immunotherapy is a modern therapeutic procedure involving usage of the person' s immune system for fighting cancer.(Hatem Soliman 2013)

4.1 Types of cancer immunotherapy

Immunotherapy can be mediated by a couple of ways:

- Stimulation of patients own immune system to work harder to attack cancer cells. E.g. prostate cancer
- The patients are given immune system components. Example- man made immune system proteins.

This type of immunotherapy is also known as biologic therapy or biotherapy. Alternatively, cancer immunotherapy can be sub-grouped as –

- Passive immunotherapy – It requires administration of immune system components that are made outside of the body and given to patients to provide immunity against cancer.
- Active immunotherapy - It is a type of immunotherapy that tries to stimulate the host's intrinsic immune response to a disease.
- Cancer vaccines - They help to educate the immune system to recognize and destroy cancer cells (Jianda Yuan 2016)

4.1.1 Passive immunotherapy

Passive immunotherapy is comprised of immune system components that are made outside of the body (i.e. in the laboratory) and administered to patients to provide immunity against cancer. Eg. monoclonal antibodies. Monoclonal antibodies are man- made and very useful in cancer treatment because they are designed to act very specifically to cancer cells. This treatment has provided a lot of successful measures for breast cancer metastasis, e.g. trastzumab, pertuzumab and trastzumab emtansine (T- DM1). Trastuzumab and pertuzumab targets HER2 receptors in breast cancer. Trastuzumab is beneficial for both node-positive and high risk node-negative breast cancer patients.(Ada Funaro 2013) The antibody pertuzumab is now given in a combination therapy with trastuzumab. T-DM1 is a combination of trastuzumab antibody and cytotoxic agent, serves standard care to the patients having resistance to trastuzumab. Combination therapy of multiple mAbs sometimes tend to take advantage of their synergistic properties. Several data show that Phase II trials of pertzumab/tratuzumab combination therapy is well-tolerated and have a good response rate worldwide. Despite the success of trastuzumab, different tumor resistance remains a major obstacle in cancer care. Combination of an antibody with a cytotoxic agent have seen to maximize the efficacy of the drug minimizing exposure to normal tissues.(Ira Mellman 2011)

Some of the limitations of monoclonal antibodies are as follows

- Many monoclonal antibodies cannot be administered as first-line therapy they are generally administrated as second line of therapy.
- Not all antigens are the same: All cancers may "look" the same, but they are not. Not all patients' cancers may express the antigen against which a specific monoclonal antibody is targeted.
- Tumor cells mutate as a result of chemotherapy and radiation treatment, and therefore the target antigen on the tumor cell at which the therapy is aimed also can be changed.
- Toxicity associated with some targeted therapies can be significant.(www.cancer.net)

4.1.2 Active immunotherapy

Active immunotherapy tries to stimulate the host's intrinsic immune response to a disease. Eg. immune checkpoint inhibitors, cancer vaccines.

4.1.2.1 Immune checkpoint inhibitors

These are a kind of drugs that generally helps in the taking of ‘ brakes’ off the immune system. They help in recognition of cancer cells and attack them. One strategy is the blockade of inhibitory receptors such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death (PD-1). Cytotoxic T lymphocytes (CTLs) normally recognize and destroy tumor cells. However, inhibitory mechanisms exist that interrupt this mechanism. Modulating such regulators of immunity such as regulatory T cells (Tregs) and immune checkpoint pathways are novel methods of active immunotherapy with great therapeutic potential.(Erika Schenble, 2015)

Some of the limitations of immune checkpoint inhibitors are -

- most cancer vaccines are targeted
- Not all antigens are the same
- Tumor cells are mutated. (www.cancer.net)

4.1.2.2 Cancer vaccines

Cancer vaccines are active and specific immunotherapeutic approach. Provenge (sipuleucel-T), is the first cancer vaccine which gained FDA approval for the treating hormone-resistance metastatic prostate cancer in 2010. No cancer vaccine till date is approved for the treatment of breast cancer. Cancer vaccine is supposed to serve to those patients having high chance of recurrence of cancer after primary treatment. These vaccines generally target immunogenic cancer-related antigens for targeting cancer- related epitopes which are over-expressed on malignant tissue but are different from normal tissue, this is how they stimulate a person’ s own immune system against cancer and they show tumour specificity by showing immune response to a particular tumour specific antigen. The key advantage of vaccines is the capability of showing response to a particular cancer or tumour even long after the completion of treatment. An ideal vaccine always tends to stimulate activation and proliferation of specific lymphocytes thus stimulating both humoral and cellular immunity. (Erika Schenble, 2015)

Some of the examples are as follows -

- HER2 vaccine development: HER2 targeting breast cancer vaccine includes several peptide, protein, plasma DNA, and dendritic based vaccines The earliest trials of this vaccine were only having single epitope peptide. Initial formulation strategies were to include emulsified immunoadjuvant or pulsation with dendritic cells. Recent trials are more focused on utilization of longer and/or multiple peptide sequences designed to produce a more effective, complete immune response. The main challenge of this treatment is to find ideal tumor associated antigen (TAA). The goal of this kind of treatment is to create more personalized and specific vaccine therapy.
- Nelipepimut-S: It is a nine amino-acid peptide. It is present in extracellular domain of HER2 and is characterized by HLAA2 restriction. It has a peptide-based strategy. This drug can be administrated with simplicity and monitoring also have the ability to use the immunodominant epitope in combination with other antigens or sometimes alone. The trials demonstrated the peptides are safe and capable of producing a peptide-specific CTL immune response in metastatic breast cancer patients. Recently different clinical trials of nelipepimut-S + GMCSF (NeuVaxTM, Galena Biopharma, Portland) had been proven to have effects on clincal issues outside the metastatic setting.(Henrique Neves 2015)

Limitations of cancer vaccines:

- Cancer cells suppress the immune system. In this way the cancer cells are able to develop and grow in the first place. Adjuvants are used in vaccines to get rid of this problem.
- Cancer cells develop from a person’ s own healthy cells, so it becomes difficult to isolate normal cells from cancer cells.
- Larger or more advanced tumors are hard to get rid of using only a vaccine.

- People who are sick or older can have weak immune systems.(www.cancer.net)

4.2 Advantages of immunotherapy over traditional chemotherapy and radiotherapy

Cancer immunotherapy can work on many different types of cancer (Sofia Farkona 2016)-

- Immunotherapy enables the immune system to recognize and target cancer cells, making it a universal answer to cancer
- Immunotherapy has been an effective treatment for patients with certain types of cancer that has become resistant to chemotherapy and radiation treatment.

Cancer immunotherapy offers the possibility for long-term cancer remission -

- Immunotherapy can " train" the immune system to remember cancer cells. This " immunomemory" may result in longer-lasting remissions
- Clinical studies on long-term overall survival have shown that the beneficial responses to cancer immunotherapy treatment are durable—that is, they can be maintained even after treatment is completed

Cancer immunotherapy may not cause the same side effects as chemotherapy and radiation -

- Cancer immunotherapy is focused on the immune system and is often more targeted than conventional cancer treatments such as chemotherapy or radiation
- Both chemotherapy and radiation damages healthy cells, leading to common side effects such as hair loss and nausea/vomiting. These side effects may be less likely with immunotherapy.

They are usually related to stimulation of the immune system and can range from minor symptoms of inflammation (eg, fever).

V. IMMUNOGENIC EFFECT OF STANDARD TREATMENT OF BREAST CANCER

Current treatments in breast cancer trigger immunologic changes within the tumour microenvironment. Several data suggest that these changes have a direct contribution to the efficacy of these treatments. The certain chemotherapeutic agents like anthracyclines and platinum salts have ability to induce " immunogenic cell death" (Zitvogel). These agents trigger the release of inflammatory " danger signals" within the tumour like high- mobility group box 1 (HMGB1) and adenosine triphosphate (ATP). These signals can start a cascade of immune activation through IL-1β secretion and activation of Toll ligand receptor 4 (TLR4) on infiltrating dendritic cells. Calreticulin is a phagocytic signal for dendritic cells for commanding them to take up apoptotic bodies and process associated tumor antigens for presentation. Trastuzumab given to HER2-amplified breast cancer patients are involved in downregulation of signalling through HER2 heterodimer- activated pathways. It also activates antibody-dependent cytotoxic cellular (ADCC) which can kill of HER2-overexpressing cells via natural killer (NK) cell activation. The importance of ADCC in the outcomes of patients with metastatic breast cancer treated with taxanes plus concurrent trastuzumab, the polymorphisms in the immunoglobulin G fragment C-γ (IgG Fcγ) receptor genes of patients. This receptor on NK cells docks with the IgG Fc portion of trastuzumab and activates NK cells to kill tumor cells. They include the upregulation of major histocompatibility complex (MHC) class I expression, release of chemokine (C-X-C motif) ligand 16 (CXCL16), and presentation of radiation-induced tumor epitopes .The combination of radiation and a cytotoxic leukocyte antigen 4 (CTLA-4) agonist can trigger a potent enough immune response that in some cases may shrink other metastatic tumors outside of the radiation field. Exploiting this abscopal effect by using the radiated primary tumor as an antigen source to provoke a potent systemic antitumor response augmented by chemotherapy and immunomodulators would be an intriguing treatment approach for neoadjuvant or denovo metastatic breast cancer patients.(Hatem Soliman, 2015)

VI. IMMUNOGENICITY OF BREAST CANCER

The interaction between the immune system and malignant tumors is a major focus of current phase of cancer research. First clinical trials of immune checkpoint inhibitors like anti-PDL1, anti-PD1 or anti-CTLA4-antibodies show comparatively high response

rates in malignant melanoma. For this new therapeutic approach, we need to find the factors that show evidence of immunogenicity, the ability to induce an immune response.

Breast cancer is not referred as typical immunogenic tumor traditionally but the disease is well known for a heterogeneous mixture of different molecular subtypes. It also has tumor-infiltrating lymphocytes that respond to neoadjuvant chemotherapy. Study shows that the presence of CD8+ T cells in breast cancer tissue was chiefly associated with a 28% reduction of breast cancer-specific mortality in ER-negative tumors. In some study two different immune markers are evaluated: CD8 as a marker of antitumor cytotoxic activity, and FOXP3 as a marker of T-regulatory lymphocytes. This FOXP3 can sometimes exert an immunosuppressive effect in the tumor microenvironment. CD8 was clearly linked to an improved survival in ER-negative tumors and ER-positive/HER2+ tumors. Some study show that certain subtypes of breast cancer like ER-negative and ER-positive/HER2-positive tumors show evidence of a relevant tumor– immune interaction (Ali et al 2013).

VII. CONCLUSION

Present day advance breast cancer requires new and more equipped medicine. It needs to be personalized too. In order to find out new methods of treatment, immunotherapy evolved. Immunotherapy is a very modern approach to battle against cancer. It helps in boosting of a person' s own immune system. As previously discussed chief measures of immunotherapy are – monoclonal antibody therapy, cancer vaccines and immune checkpoint blockade therapy.

Some other approaches to treatment of breast cancer involves the use of oncolytic virus therapy. Oncolytic viruses are viruses that directly kill (" lyse") cancer cells and can also activate cells of the immune system, such as dendritic cells and T cells, to target and eliminate cancer throughout the body. An example is talimogene laherparepvec (Imlygic), which is an oncolytic virus that has been modified to make GM-CSF, a protein that boosts the immune response. This virus can be used to treat melanomas in the skin or lymph nodes. Oncolytic virus immunotherapies are currently being studied in clinical trials for a number of cancers, such as CG0070 (bladder cancer), reolysin (prostate, colorectal, ovarian, lung, and breast cancer), CAVATAK (melanoma), JX-594 (ovarian cancer), MV-NIS (multiple myeloma), T-VEC (melanoma).(www.cancer.net)

Another approach is the use of adoptive T cell transfer technology. It is an anti-cancer approach that enhances the natural cancer-fighting ability of the body' s T cells by removing immune system cells, growing and/or making changes to them outside of the body, and then re-infusing them back into the patient. Although, no adoptive T cell transfer technique is FDA approved, but several have shown great promise in early clinical trials of metastatic melanoma, lymphoma, leukemia, neuroblastoma, and synovial cell sarcoma; it is currently being investigated for use in other solid tumors.

Also, cytokines have been in clinical trials for cancer therapy. Cytokines are messenger molecules that help control the growth and activity of immune system cells, as well as blood cells. Types of cytokines include interleukins (IL), which help immune cells grow and divide more quickly; and interferons (IFN), which boost the ability of certain immune cells to attack cancer cells. IFNA has been in clinical trial for renal cancer, melanoma, Hairy cell leukemia , follicular non-hodgkin' s lymphoma, cutaneous T cell lymphoma, chronic myelogenous leukemia, Kaposi' s sarcoma.

Adjuvant immunotherapies are substances that are either used alone or combined with other immunotherapies to boost the immune response even more. Bacillus Calmette- Guérin (BCG) is FDA approved to treat superficial bladder cancer. Granulocyte macrophage colony-stimulating factor (GM-CSF) is a cytokine that stimulates dendritic cells to develop, and is often used as an adjuvant with therapeutic cancer vaccines, including those for prostate and pancreatic cancer. An adjuvant immunotherapy called Montanide is currently being used in vaccine trials for a number of cancers. Toll-like receptors (TLRs) are used to enhance the body' s immune response, and have shown effectiveness in brain, kidney, lung, colon, pancreatic, prostate, ovarian and breast cancer.(https://www.cancer.org)