Immunotherapy in Breast Cancer Treatment

Jianfei Luo

Ulink College of Shanghai, 559 South Laiting Road, Jiuting Town, Songjiang District, Shanghai, 201615, China
Corresponding Author: Jianfei Luo, Email: AlphaH2SO4@outlook.com

Abstract

Breast cancer is widely common among the female cancer patients. The illness brings women inconveniences or even takes away their lives and tears thousands of families apart. Fortunately, academic and clinical researches are discovering therapies to ease the suffering of the ones being diagnosed of breast cancer. One of the newest ways includes immunotherapy. Though this technic is still in development, there is great potential that it may benefit the patients and alleviate their pain in comparison with other regular treatments. In order to know how this therapy works, this paper first carries out an analysis of breast cancer itself (such as its classification, reasons causing it or its diagnosis). And then the focus is put on the immunotherapy specifically. The paper also compares immunotherapy with other traditional treatments for breast cancer and discusses the combination of other therapies with immunotherapy. As can be expected, there are many factors in real life that may affect the curative effect of this treatment that give rise to side effects. Therefore, the pros and cons of using the immunotherapy on patients are analyzed and evaluated. Another factor that is considered is how patients get access to treatments of immunotherapy, especially financially. With all these aspects taken into consideration the paper makes a prediction of how immunotherapy may work in the future in the treatment of breast cancer, as well as how the treatment can be used both effectively and affordably to patients.

Keywords

Breast cancer; Breast cancer treatment; Immunotherapy

Introduction

Cancer is a worldwide illness, leading to millions of deaths every year. Among all types of cancer, breast cancer has a relatively high diagnosis rate. According to the World Health Organization, in the year 2020, around 2.3 million women all over the world were being diagnosed as breast cancer while 685,000 of them died because of it. The high incidence and mortality rate is a non-negligible big source of anxiety for numerous women, and is a big health concern. Thus, it is quite significant to find out more treatments for breast cancer.

Citation: Jianfei Luo. (2022) Immunotherapy in Breast Cancer Treatment. The Journal of Young Researchers 4(9): e20220531

Received on May 7, 2022; Accepted on May 10, 2022; Published on May 31, 2022

The cancers are quite closely related to our bodies' immune system which detect both exogenous pathogens and endogenous mutated cells. Unfortunately, the cancer cells have developed various mechanisms which prevent the immune system from destroying them, either escaping the surveillance of the immune cells, or inactivate them so that our own bodies do not have the ability to destroy these harmful cells which then lead to devastating consequences. With the development of medicine and discovery from research, some methods have been developed to fight against cancer with some success. For example, certain types of breast cancer have 90% of survival rate without relapse. The Surveillance, Epidemiology, and End Results (SEER) database listed the survival rates for different types of cancer, including breast cancer. According to it, patients with breast cancer but no metastases have the survival rate of 99% in five years. Patients diagnosed of breast cancer which spreads to nearby lymph nodes have a survival rate of 86% and most unfortunately, the ones with breast cancer which has spread to other organs such as lungs, only have a surviving rate of 29%. Taking into account of all the cases, the average survival rate is about 90%, which is quite high compared with other types of cancer. Therefore, it is still necessary for people and experts to keep on looking for the new cures for these illnesses as the present treatments still have their own drawbacks which haunt the patients and bring them inconvenience in their daily life during the treatment of cancer or even after the treatment of cancer. Breast cancer can still be lethal due to the lack of effective treatments. Therefore, finding out new ways to treat breast cancer is of urgent need.

Recent research has found out a new way of treating cancers (including breast cancer) and is showing effective result and promising future. Thus, this paper aims to introduce types of breast cancer, factors causing them, diagnosis of breast cancer, common therapies of breast cancer, specifically immunotherapy (their usage in breast cancer), as well as how immunotherapy can be combined with other general therapies, advantages and disadvantages compared with other therapies and how to make immunotherapy affordable for patients.

Classification of Breast Cancer

Breast cancer can be divided into five different surrogate intrinsic subtypes as shown in Fig. 1. They are mostly classified according to whether certain receptors are being expressed on the surface membrane. These receptors include estrogen receptor (ER), human epidermal growth factor receptor 2 (HER 2) and progesterone receptor (PR). Based on the differences between the receptors the breast cancers are divided into triple negative, HER2-enriched, Luminal B-like HER2+, Luminal B-like HER2–, Luminal A-like respectively.

Triple negative: triple negative breast cancer (TNBC) is the breast cancer which does not have ER, PR or HER2 on their cell membrane. They are supposedly the type of breast cancer hardest to be treated due to their lack of receptors on the surface for other drugs or immune cells to pair with and is hard to detect or destroy them.

HER2-enriched: this is the type of breast cancer which amplifies the HER2, but ER and PR both present a negative result.

Luminal B-like HER2+:This type of tumor cells has ER, PR and HER2 expressing. However, the ER and PR have lower expressions.

Luminal B-like HER2– Luminal B-like HER2– is almost the same as the Luminal B-like HER2+, except for the HER2, where it has negative expression of HER2 on the surface membrane.

Luminal A-like: compared with the previous two subtypes of breast cancer, Luminal A-like has expressed the ER and PR much stronger than Luminal B-like HER2+ and Luminal B-like HER2– do, but HER2 is not expressed in Luminal A-like.

Going down the list of breast cancer subtypes provided above, certain different trends can be witnessed，for example, their multiplication or proliferation decreases. As shown in Fig.1, TNBC, has less receptors and is hard to be destroyed by drugs or our immune system and will cause higher risk of a rise in the number of tumor cells than the other subtypes whereas subtypes of breast cancer such as Luminal A-like can be detected much more easily as they have features which are extremely outstanding. TNBC and HER2-enriched are both 'basal-like' as they have more mutations, causing the changes of the receptor and making them even harder to detect. In addition, the decreased ability in differentiation raises the possibility of turning into malignant cancer. More details about their trend are that the ER expression increases down the list of subtypes written above while the HER2 expression is gradually reducing (Cardoso et al., 2019).

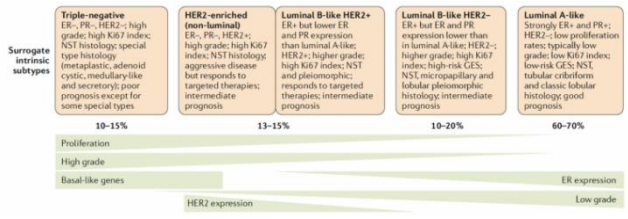

Figure 1. Classification of breast cancer and their characteristics (Cardoso et al., 2019)

Factors Causing Breast Cancer

Research shows that there are several factors underlying the occurrence of breast cancer.

Pregnancy

Research indicates that the increase in giving birth to child reduces the probability for women to develop breast cancer, especially in the PR positive and ER positive breast cancers (Ma, Bernstein et al. 2006). In that case, full-term pregnancy is seen as a factor which is protecting women from encountering with such an illness. What's most significant is that giving birth at an elder age is very likely to cause the breast cancer to develop in females. It is shown that first full-term pregnancy can reduce the risk of breast cancer by 23% (Laamiri, Bouayad et al. 2015). However, contradictory conclusion proposes that it is believed that giving birth for more than five times before the age of 45 will again raise the risk of having breast cancer development but then a decrease in such risk when the age is above 45 (Palmer, Wise et al. 2003).

Hereditary

Another risk that is the main cause of breast cancer is heredity since breast cancer may be highly associated with the mutations in genes. If genes are involved in this carcinoma, it is most likely caused by the mutation of BRCA1 or BRCA2. About 40 out of 100 people who are diagnosed of breast cancer have mutations in either of these genes (Cobain, Milliron et al. 2016). Though not every BRCA1 and BRCA2 gene mutation carriers will have the development to breast cancer, still around 60% of females who have mutated BRCA1 and 45% of women with mutations in BRCA2 will have breast cancer in their 70s (Godet and Gilkes 2017). It was found out that if a family has two women under the age of 50 and are diagnosed as breast cancer and have been negative in BRCA, the chance for other women in this family to develop breast cancer is 11 times higher than normal female (Metcalfe, Finch et al. 2009).

Working at Night

Working during the night highly increases females' risk of developing breast cancer, especially for the ones that have been doing

such work for over two decades (Benabu, Stoll et al. 2015). This is due to the reduction in the production of melatonin which causes people's body to develop a huge amount of hormones and leads to the breast cancers that are susceptible to hormones (Kerenyi, Pandula et al. 1990).

Coffee

Different researches have reached different conclusions in the effect of coffee on breast cancer. For instance, there are studies of some cases show among postmenopausal females who have the habit of drinking coffee, there is a decrease in the probability of being diagnosed of ER-negative breast cancer (Li, Seibold et al. 2011); in other case studies, it is argued that there is less ER positive and PR negative breast tumors detected in the women who drinks coffee (Oh, Sandin et al. 2015). In contrast, it is believed that the coffee drinkers who have used hormones before will cause and increase in the potential of getting breast cancer (Yaghjyan, Rich et al. 2018).

Hormone

It is shown that some women that have the habit of using hormone replacement therapy (HRT), which is a kind of drug to reduce effects brought up by the menopause, are increasing the chance of developing breast cancer (Cancer, 1997), and even has higher when they added progesterone into the HRT's treatment (Ross et al., 2000). However, research shows that it will not increase the probability of having breast cancer if the women is postmenopausal or have certain mutations in the gene BRCA1 (Collaborators, 2003).

Diagnosis of Breast Cancer

Screening is one of the ways in which we can detect the breast tumors at an early stage before the breast tumor becomes metastatic. Mammography is a kind of screening technique used specifically to provide images of the breast, to show if there are tumors growing inside the breasts. They are most effective when applied to women between ages of 50s and 60s. Less benefits of the usage of mammography will occur with the ones outside this age range (Nelson, Fu et al. 2016). Due to the ability of Mammography in detecting early breast cancers, it highly reduces the need of mastectomy (physically removing parts or the whole breast in order to stop the breast cancer from moving to other places through lymph nodes and start invading other parts of the body) (Cardoso et al., 2019). The problem of using mammography, however, is that it may cause misdiagnosis or overdiagnosis and leads to overtreatment (Nelson, Pappas et al. 2016). Tomosynthesis, which is another method of detecting breast cancer and has similar functions to mammography (the same workings as mammography but in 3D shape) can be used as well. Also, combining Magnetic Resonance Imaging (MRI) with mammography or tomosynthesis can greatly increase the detection of cancers caused by mutations in BRCA1 and mutations in BRCA2 (Saslow, Boetes et al. 2007). These methods are effective in detecting breast cancer, even at an early stage. Unfortunately, they cannot be used to evaluate the death rate of the patients (Lauby-Secretan, Scoccianti et al. 2015).

Common Therapies of Breast Cancer

Chemotherapy

Chemotherapy is used widely throughout the treatment of all sorts of cancers due to the fact that they are capable of inducing Immunogenic Cell Death (ICD) (Galluzzi et al., 2017). A variety of death signals will be released by tumor cells, (extracellular ATP, CRT, HMGB1, HSPs etc.) when they encounter with the drugs

used in chemotherapy. These signals may lead to the death of the tumors. Calreticulin (CRT), for example, expresses on the tumor cells when meeting the chemotherapy drugs and help promote the dendritic cells to act as antigen presenting cells for the T cells. Also, HMGB1 helps promote pro-inflammatory factors, interleukins interferons and so on which assist our immune system to fight against the tumor cells (Sugie, 2018).

Radiotherapy

Radiotherapy can be linked to ICD as well. In some situations, the tumors that are outside the range of radiotherapy shrink as well, just like the ones that are being cured by radiation. This is due to the danger signals sent by the tumor cells which skyrockets the T cell receptor repertoire and T cells will have higher chance of detecting the tumor cells that have mutated inside our bodies (Victor et al., 2015, Rudqvist et al., 2018).

Adjuvant Endocrine Therapy

To give a general impression of this therapy, it is the usage of different combinations of drugs and inhibitors to reduce the production of certain hormones. As we know a number of factors leading to breast cancer includes hormones and controlling them is a way to prevent the development of this carcinoma.

This therapy is generally divided into two parts, one is premenopausal while the other is postmenopausal. However, most of the therapies are similar in the use of Tamoxifen and Aromatase inhibitor. They mostly differ in the ways of combining the therapies due to different people's situation. With regards to the premenopausal part, after patients use Tamoxifen for 5 years, the therapy can still be divided into premenopausal and postmenopausal, depending on the person's age and physical condition. For the postmenopausal part, it is much simpler, where they are only divided into three ways of usage of Tamoxifen and aromatase inhibitors as shown in Fig.2.

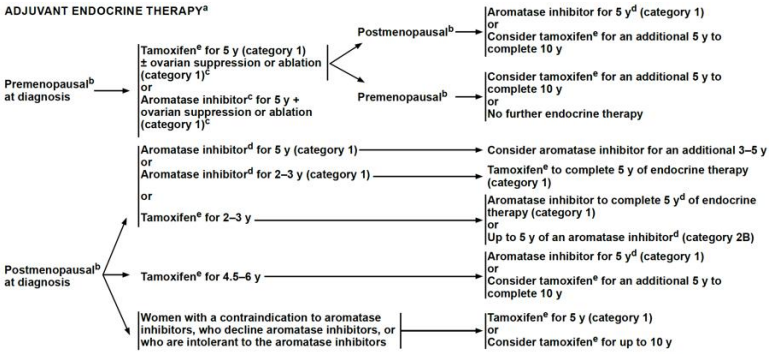

Figure 2. Guideline of adjuvant endocrine therapy (NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)

Immunotherapy

Basically, immunotherapy is a kind of treatment that can be used in eliminating cancer by enhancing our own body's immune system. Just as other pathogens, cancer cells can also be detected by our immune cells which are supposed to help us destroy these mutated cancer cells immediately. However, sometimes the cancer cells have their own ability to avoid the detection of our immune system, further leading to metastasis and growth of carcinomas in other parts of our body, fighting with the normal cells for nutrition. Thus, immunotherapy is trying to enhance the detection and making our immune system powerful enough to detect cancers by ourselves.

Immunotherapy in Breast Cancer

Immunotherapy can basically be divided into THREE parts: cancer vaccines, adoptive cell transfer, immune checkpoint inhibitors. However, different therapies can be used to treat different types of breast cancer, depending on their characteristics such as fluidity, receptors on the surface of the tumor cells etc. the following sections will introduce them respectively.

Cancer Vaccines

HER2 Peptide Vaccines can be used to increase the immunity which exists in the body already. E75 peptide and GP2 peptide are its main target. However, the polypeptides are exclusive to HLA-A2+ patients which contributes to half of the population in the USA (Clive et al., 2012, Sinn et al., 2013).

MUC1 Peptide Vaccines can also be used. MUC1 is an antigen which will be over expressed in breast cancer as well as other types of cancers. Biomarkers (CA27.29 and CA15-3) are targeting MUC1 and may be used to fight against breast cancer (Blixt et al., 2011). Sialyl-Tn (STn) is an epitope on MUC1 made out of carbohydrate. It is responsible for the metastasis and growing of the breast cancer tumor cells (Julien et al., 2009). Experts are designing vaccines such as Theratope to mimic the STn so that the theratope is able to combine with the heavy carrier protein keyhole limpet hemocyanin (KLH) before putting them together with Detox B which is a kind of adjuvant (MacLean et al., 1993). In that case, it becomes a way to help cure the cancer. Unfortunately, research into the theratope has not yet improved the survival time of patients. However, it has promising results that the survival rate increases with the patients that are undergoing endocrine therapy which may lead to the combination of these two therapies (Ibrahim et al., 2013).

Cancer-Testis (CT) Antigen Vaccines can be used in ER negative cancers. These cancers have an over expression of CT antigens and have relatively high immunogenicity (Page et al., 2014) and these antigens act as targets for breast cancer (Theurillat et al., 2007).

Breast Cancer Target Antigens Carcinoembryonic antigen (CEA) is a glycosylated protein and is expressed within a number of cancers and vaccines are able to be developed targeting this antigen (Thompson et al., 1991).

Telomerase (hTERT) are expressed in most cancers where they are used to repair telomere. Vaccines produced lead to anti-tumor immunity (Parkhurst et al., 2004).

We could also pay more attention to the Wilms' tumor antigen (WT1) which is a protein for transcription and differentiation, apoptosis as well as proliferation are being controlled by it (Cheever et al., 2009). Adjuvants such as Montanide ISA are being used in trials together with the WT1 (Morita et al., 2006).

Mammaglobin-A (Mam-A) is being over expressed in approximately 80% of all the breast cancers that have metastasized. Fortunately, a trial of Mam-A DNA vaccine has being used to help CD4+ICOS T cells be produced by IFN-γ which can kill tumors (Tiriveedhi et al., 2013).

Cellular vaccines are multivalent vaccines. They contain tumor cells or dendritic cells that are fused with tumor cells. They also contain lysate of tumors or the genetic materials of cancer such as RNA or DNA (Melero et al., 2014).

Adoptive Cell Transfer

Adoptive cell transfer mainly includes the CAR-T cell therapy, where T cells of patients are acquired and genes are edited so they have Chimeric Antigen Receptor (CAR). After a huge number of T cells are accumulated, they are infused back into the patients and can help fight cancer.

FC γ Receptor (FCγR) has the ability to redirect T cells to almost any tumor cell expressing antigen. Parts of this receptor CD16A and CD32A have the ability to produce CAR-T Cells where CD16 is usually present on NK

cells and CD32 is usually on monocytes, macrophages, dendritic cells and NK cells. Also, they have different affinity to bind to the antibodies (Anania et al., 2019). Meanwhile, just as shown in Figure 3, ADCC and target cell depletion may occur when the two receptors contact with the Fc region of the various antibodies (Dees et al., 2020).

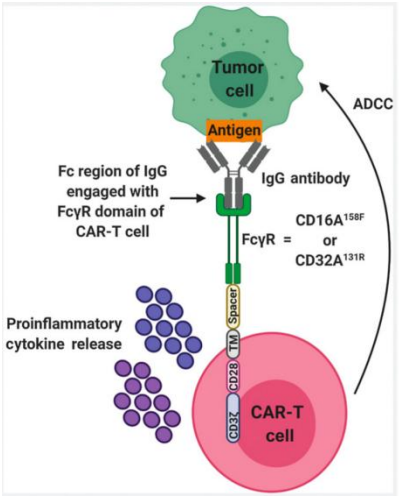

Figure 3. Adoptive cell transfer mechanism (Grewal et al., 2020)

Also, the ADCC activity depends on the different types of antibodies. For instance, IgG1 and IgG2 are used to cure EGFR positive tumors. However, human's IgG2 has a low affinity towards CD16 which leads to low activity of ADCC. In contrast, the ADCC activity is high when wither of the antibodies is linked with CD32 and EGFR is overexpressed in TNBC (Liu et al., 2019). In that case, this could be a potential way for us to treat TNBC in target. What's more, these two antibodies have the ability to neutralize the proinflammatory cytokinesis such as IFNγ and TNFα, achieving the optimum tumor cytotoxicity (Caratelli et al., 2020).

Chondroitin sulfate proteoglycan 4 (CSPG4) is expressed on the TNBC which makes it a good receptor. CSPG4-CAR-T cell is able to inhibit the growth of tumor cells (Harrer et al., 2019). However, the second generation in vitro found out that the anti-tumor activity which may lead to the death of tumor cells causes the release of pro inflammatory cytokines. Thus, suicide genes need to be inserted into CSPG4-CAR-T Cell which will lead to cell death after the activity to stop toxicity harming the human body (Beard et al., 2014).

As mentioned before, EFGR is a receptor that is over expressed in 45% to 70% of patients with Triple Negative Breast Cancer. EGFR-CAR-T Cells like other CAR-T Cells, have the ability to inhibit tumor cell growth (Liu et al., 2019). What is significant about it is that the EGFR variant III on the tumor cells is tumor rescripted which leads to a lower on-target or off-tumor toxicity (Heimberger et al., 2005).

Immune Checkpoint Inhibitors

Immune checkpoint is basically the pathways of various signals that will help mediate the immune response in our bodies. In other words, they are here to control the immune system from being out of control or attacking our own body. However, the tumor cells take it as advantage and find ways to escape from our immune system and thus start developing at high speed without any obstacles stopping them. It is necessary for us to know what is immune checkpoint in the first place. T cells have the ability to cause humoral immune response by linking their receptors to body cells' surface membrane. To avoid the T cells from attacking the body's own cells, there are receptors on the T cell and on the body's cells and they can link with each other, informing the immune cells not to attack its own body. Usually, the receptors are PD-1 (also known as CD279) and PD-L1 (also known as CD 274). PD-1 is the receptor on the T cell while PD-L1 is the receptor on the body's cell. When these two receptors bind together, even if there are other receptors that connect to the cell as well which normally would cause the T cells to release perforin and break down the body's cell, the destruction

processes of the T cells will be inhibited.

Unfortunately, the tumor cells also have the PD-L1 receptor as they are seen as normal cells inside our body as well. This greatly helps the tumor cells from evading the attack of the immune system as the immune cells will see the tumor cells as normal cells which is a part of us and attacking these cancer cells will not be permitted. Thus, what people are trying to do is to use inhibitors to block the receptors from meeting each other. The most recently developed drugs used to block PD-1 (anti-PD-1 drug) which is pembrolizumab linked with axitinib (to inhibit the VEGF receptor which is used to bind with the factor causing growth of vascular endothelial). However, the con of using axitinib is that the toleration may occur due to the molecule being quite specific. In that case, it is believed that the usage of immune checkpoint inhibitor will have huge progress when more development has appeared and they can be used to overcome the drawbacks (Meric-Bernstam et al., 2021).

Studies show that the treatment of immune checkpoint inhibitor works the best with the TNBC subtype in breast cancer. Hormone Receptor–Positive Breast Cancer may be treated with immune checkpoint inhibitor as well, but may not have much responses as the treatment in TNBC. For the HER-2 positive breast cancers, they have a low response rate towards this kind of therapy or they may even have no responses (Santa-Maria & Nanda, 2018).

Other Treatments Combined with Immunotherapy

Chemotherapy

With immune checkpoint inhibitors combining immune checkpoint inhibitors with other drugs is a choice. For instance, in TNBC, atezolizumab (a kind of drug which is able to prevent the receptors on the T killer cells and the receptors on the tumor cell from binding together) is combined with certain drugs used in chemotherapy, such as abraxanevs. This combination greatly reduces the mitosis and more antigens on the tumor is able to be released. Therefore, the effects of immune checkpoint inhibition will be enhanced. Also, taxanes are able to promote the dendritic cells which will increase the antigen being presented and thus increase our body's own immunity to fight back the tumor cells which usually develop some strategies to escape from immune surveillance.

With Cancer vaccines p53 cancer vaccines are combined with chemotherapy. This is because this gene is linked with suppression of tumor cells. The mutation of p53 is quite common among a lot of cancers, including breast cancer, and are found in most breast cancers. Thus, this gene signature is quite a good choice to be used as a vaccine to combine with chemotherapy, which again enhances its ability to fight tumor cells. In one trial tested, before taking chemotherapy, about 57.1% of the patients have responses from their T cells and when subsequently treated with drugs used in chemotherapy, 61.9% of them have responses. This shows the relation of combining chemotherapy and vaccines used in cancers clearly and effectively. They increase the responses of T cells so that they can better detect the tumor cells (Antonia et al., 2006).

Radiation

As mentioned before, the basic theory is to use radiation and increase the immunogenic cell death where they release large numbers of danger signals which have the ability to attract the T cells and help our immune system to recognize the presence of tumor cells. Antigens are presented more and T cell receptor repertoire ascends. Other molecules that may cause the co-stimulatory are produced as well. Radiation pairing up with the immune

checkpoint inhibitors are being researched. For instance, patients with HER-2 positive illness used drugs trastuzumab as well as tremelimumab combined with radiation.

Also, the effect people wanted to see when combining them together is that they can cause abscopal effect. This is when local radiation occurs they cause the tumor cells to release tumor antigens which will be picked up by antigen presenting cells (Ngwa et al., 2018). They will then move to lymph nodes where there are a lot of killer T cells. The antigen presenting cells will use MHC II to provide them with the fragments of the antigens to activate the killer T cells. Then these T cells will circulate around the body to find other tumor cells that may not only be inside the radiation area. However, due to the changes which may occur on the tumors' antigens, they can avoid the activated T cells. Thus, we need certain immunotherapy used drugs to make some changes to the T cells as well. Using drugs such as ipilimumab will reduce the effects of changes on the tumor cells' antigens. The main reason is not yet discovered; however, it is believed that when ICD occurs, they excrete chemokines and will lead to the development of other clones of T cells which also have various antigens on their surface membrane. These new T cells can become new targets of the drugs used and increase the response against tumors (Kalbasi et al., 2013).

Combining radiation with immunotherapy may have a high possibility of being used in treating in the near future in breast cancer. As breast cancer is a body surface tumor before metastasis, the radiation is able to eliminate the breast cancer relatively easily. In addition, due to the abscopal effect, many cancer cells which have transferred to other places in the body from the breast through the lymph nodes may also be eliminated. With immunotherapy, they can enhance our immune cells and help destroy these cancer cells. The Adoptive Cell Transfer which will induce the CAR-T cell therapy can possibly be combined with radiation so that we can use both strong T cells and the radiation which may initiate a lot of response when cancer cells give out danger signals.

Advantages and Disadvantages Compared with Other Therapies

Advantages

To begin with, immunotherapy has higher specificity. Unlike chemotherapy which may destroy not only the tumor cells but also the normal cells, immunotherapy is working to target against specific tumor cells. For example, the vaccines can only be used in treating the specific subtypes in breast cancer due to their difference in antigen presentation. This may lead to less side effect and does not harm our body's normal cells. In contrast, chemotherapy, for instance, may cause nausea, hair loss and reduction in the strength of one's immunity. For immunotherapy problems such as weakening of the immune system is not likely going to happen as the fundamental theory is to improve our own immune system to fight against cancers (Tan et al., 2020). However, my belief is that this opinion may need to be considered. Though some symptoms or side effects are reduced when using immunotherapy, there are other conditions occurring and may still have a lot of effects on the patients.

In addition, immunotherapy can be used to eliminate the cancers fully compared with other therapies. Treatments such as mastectomy in breast cancer is not able to clear all the breast cancer cells when metastasis occurs (Tan et al., 2020).

Disadvantages

However, the treatments have their own weaknesses and areas that require improvement. Just as mentioned above, there might be other

effects occurring. For example, the immune checkpoint inhibitor may lead to autoimmune disease as when stop regulating the T cells in our bodies, they may start attacking the normal cells inside us (Tan et al., 2020).

Toxicity may be a concern when using combinations of different therapies with immunotherapy as well. For instance, a drug called vemurafenib is forbidden to be used with ipilumumab due to the toxicity that is produced when used together. Also, the patients may try to use combination of therapies with immunotherapy to prevent a certain number of unknown effects on the tumor microenvironment. This perhaps will lead to ascending toxicity in one's body (Tan et al., 2020).

The cost of immunotherapy is a factor which prevents patients from using the treatment. Usually, it costs each patient $60,000 to be treated with CAR-T. The reason for immunotherapy being so expensive is that it has high specificity and the treatment will be customized for individuals. For example, CAR-T requires genetic engineering of one's own T cells and this already needs around 21 days of working in the laboratory. Also, getting genetically modified T cells requires high technology, professional labs and experts that are familiar in this field. All of the high requirements will definitely rise the price of the treatment. What's more, usually the treatment will not only be immunotherapy it will be most likely that immunotherapy is combined with another therapy and will for sure double or even triple the prices in treating or curing the cancer. Last but not least, the cost of treating cancer, no matter what therapies are used, is commonly quite high (see link).

Table 1 Advantages and limitations of immunotherapy (Tan et al., 2020)

Advantage of using immunotherapy	Limitations of using immunotherapy
1. Specificity is relatively high compared with other ways of treatment	1. Autoimmune disease may occur due to the decreasing in control of our immune system
2. Less side effects (to be considered)	2. Toxicity
3. Can eliminate cancer cells fully in theory (relatively speaking)	3. High cost, making it unaffordable for a large number of patients

By comparing the pros and cons of immunotherapy, it can be found that though there are certain drawbacks that are acting as obstacles on the way of developing immunotherapy, the benefits still exceed the disadvantages. In terms of the advantages, they have provided higher specificity and can help target specific cells to interact. Unlike chemotherapy, which may affect a large number of cells, no matter normal or tumor ones. If we use the immunotherapy, they can prevent unnecessary damages towards our normal body parts. Using immunotherapy can help reduce a lot of invalid processes and treatments on the patients.

Compared with the cons of immunotherapy, the pros still outweigh the disadvantages. For instance, though it is true that the cost of immunotherapy is high, it is undeniable that most of the therapies in cancer treatment is expensive and immunotherapy is not a single case. And all of the other drawbacks could expect to be solved since this treatment is still not popular among patients. There must be certain ways to avoid the disadvantages or to prevent them as this therapy develops.

Future Development of Immunotherapy

To improve immunotherapy in the future, we need to know more about how the cancer, its living environment and our body's immune

system interact so that biomarkers can be developed in order to acquire more information about how the immunotherapy will benefit us.

Also, as breast cancers are relatively silent immunologically, we can find ways to make them more active and can be detected more easily by our immune cells. Classification of the breast cancer can help improve our usage of immunotherapy as well as different breast cancer subtypes may lead to various therapies and may have different combinations of therapies. Thus, knowing more about the classification may help improve the effects of treatments or getting rid of the unnecessary or redundant treatments for certain breast cancer patients. For instance, combinations of different therapies are highly required in TNBC treatments. This is due to the fact that the responding time using immunotherapy is relatively long, compared with chemotherapy, and TNBC develops quite fast and furiously. Thus, combinations may be needed to treat TNBC and other the cancers that develop with a fast pace (Santa-Maria & Nanda, 2018).

Based on past research, this treatment is very promising and it will be used more in the future due to their advantages, such as high specificity (mentioned above). They are able to bring every patient his or her own individualized treatment. For example, the adoptive cell transfer is able to design specific types of immune cells for one patient and must have high effectiveness in treating cancer. The treatment available now for every patient are common and general not personalized, but due to differences in people's physiques, patients may have various problems caused by the treatment which is not suitable for their body. With immunotherapy, the designed immune cells or drugs may become more appropriate for each cancer patient.

The immunotherapy is newly developed and as a treatment of cancer, it is expensive and unaffordable to many patients. The first important thing that can help reduce the expensive price of immunotherapy is to do more investigations and research in this field. For example, more research could be done in obtaining more apparatus used in treatment. Also, more about the genetic information about the immune cells can be studied so that treatments such as adoptive cell transfer can become more mature and the production of these strong cells can be quicker and more effective and may be less costly. Some countries, such as the UK, have free medical service for their local residents and perhaps the scarcity in medical resources is the essential problem. If the technology of the therapy is mature and well developed, their efficiency may also be raised and can reduce the urgent problems caused when people are desperate in these life-saving medical services while hospitals are not able to offer them the treatment.

Also, insurance can be used to cover this therapy and the cost can be distributed. A huge number of people can each put little amount of money and obtain the funds to help the ones who need this treatment. Though it has nothing to do with the enhancement of technology used in immunotherapy, a group of people that could not afford to pay for the treatment of immunotherapy will be guaranteed to access such a treatment for cancer.

Conclusion

All things considered, it is highly possible to use different kinds of immunotherapy strategies in various cancers, including breast cancers. Though a huge number of other treatments are relatively mature, immunotherapy is also developing at high speed which may one day bring a new kind of treatment to the patients and can be more efficient, effective, accurate and has less side effects to reduce the suffering and difficulties of patients. Despite all of the drawbacks that haven't being solved yet by

experts, this newly arising therapy has its unique way of treatment in patients and help relieve symptoms or even cure patients from cancers by exploring through a different angle. Taking into consideration its well-developed theories and its own advantages, there is an optimistic outlook for this treatment and the successful usage of immunotherapy in clinical trials can be expected.

Conflict of Interests: The author has claimed that no conflict of interests exists.

References

1. Anania, J. C., Chenoweth, A. M., Wines, B. D., & Hogarth, P. M. (2019). The human FcγRII (CD32) family of leukocyte FcR in health and disease. *Frontiers in immunology*, *10*, 464.
2. Antonia, S. J., Mirza, N., Fricke, I., Chiappori, A., Thompson, P., Williams, N., Bepler, G., Simon, G., Janssen, W., & Lee, J.-H. (2006). Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. *Clinical Cancer Research*, *12*(3), 878-887.
3. Beard, R. E., Zheng, Z., Lagisetty, K. H., Burns, W. R., Tran, E., Hewitt, S. M., Abate-Daga, D., Rosati, S. F., Fine, H. A., & Ferrone, S. (2014). Multiple chimeric antigen receptors successfully target chondroitin sulfate proteoglycan 4 in several different cancer histologies and cancer stem cells. *Journal for immunotherapy of cancer*, *2*(1), 1-11.
4. Benabu, J., Stoll, F., Gonzalez, M., & Mathelin, C. (2015). Night work, shift work: Breast cancer risk factor? *Gynecologie, obstetrique & fertilite*, *43*(12), 791-799.
5. Blixt, O., Bueti, D., Burford, B., Allen, D., Julien, S., Hollingsworth, M., Gammerman, A., Fentiman, I., Taylor-Papadimitriou, J., & Burchell, J. M. (2011). Autoantibodies to aberrantly glycosylated MUC1 in early stage breast cancer are associated with a better prognosis. *Breast Cancer Research*, *13*(2), 1-16.
6. Cancer, C. G. o. H. F. i. B. (1997). Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. The Lancet, 350(9084), 1047-1059.
7. Caratelli, S., Arriga, R., Sconocchia, T., Ottaviani, A., Lanzilli, G., Pastore, D., Cenciarelli, C., Venditti, A., Del Principe, M. I., & Lauro, D. (2020). In vitro elimination of epidermal growth factor receptor-overexpressing cancer cells by CD32A-chimeric receptor T cells in combination with cetuximab or panitumumab. *International journal of cancer*, *146*(1), 236-247.
8. Cheever, M. A., Allison, J. P., Ferris, A. S., Finn, O. J., Hastings, B. M., Hecht, T. T., Mellman, I., Prindiville, S. A., Viner, J. L., & Weiner, L. M. (2009). The prioritization of cancer antigens: a national cancer institute pilot project for the acceleration of translational research. *Clinical Cancer Research*, *15*(17), 5323-5337.
9. Clive, K. S., Tyler, J. A., Clifton, G. T., Holmes, J. P., Ponniah, S., Peoples, G. E., & Mittendorf, E. A. (2012). The GP2 peptide: A HER2/neu-based breast cancer vaccine. *Journal of surgical oncology*, *105*(5), 452-458.
10. Cobain, E. F., Milliron, K. J., & Merajver, S. D. (2016). Updates on breast cancer genetics: Clinical implications of detecting syndromes of inherited increased susceptibility to breast cancer. Seminars in oncology,
11. Collaborators, M. W. S. (2003). Breast cancer and hormone-replacement therapy in the Million Women Study. *The Lancet*, 362(9382), 419-427.
12. Dees, S., Ganesan, R., Singh, S., & Grewal, I. S. (2020). Emerging CAR-T cell therapy

for the treatment of triple-negative breast cancer. *Molecular Cancer Therapeutics*, *19*(12), 2409-2421.

13. Galluzzi, L., Buqué, A., Kepp, O., Zitvogel, L., & Kroemer, G. (2017). Immunogenic cell death in cancer and infectious disease. *Nature Reviews Immunology*, *17*(2), 97-111.
14. Godet, I., & Gilkes, D. M. (2017). BRCA1 and BRCA2 mutations and treatment strategies for breast cancer. *Integrative cancer science and therapeutics*, *4*(1).
15. Harrer, D. C., Dörrie, J., & Schaft, N. (2019). Cspg4 as target for CAR-T-cell therapy of various tumor entities–merits and challenges. *International Journal of Molecular Sciences*, *20*(23), 5942.
16. Heimberger, A. B., Hlatky, R., Suki, D., Yang, D., Weinberg, J., Gilbert, M., Sawaya, R., & Aldape, K. (2005). Prognostic effect of epidermal growth factor receptor and EGFRvIII in glioblastoma multiforme patients. *Clinical Cancer Research*, *11*(4), 1462-1466.
17. Ibrahim, N. K., Murray, J. L., Zhou, D., Mittendorf, E. A., Sample, D., Tautchin, M., & Miles, D. (2013). Survival advantage in patients with metastatic breast cancer receiving endocrine therapy plus sialyl Tn-KLH vaccine: post hoc analysis of a large randomized trial. *Journal of Cancer*, *4*(7), 577.
18. Julien, S., Picco, G., Sewell, R., Vercoutter-Edouart, A., Tarp, M., Miles, D., Clausen, H., Taylor-Papadimitriou, J., & Burchell, J. (2009). Sialyl-Tn vaccine induces antibody-mediated tumour protection in a relevant murine model. *British journal of cancer*, *100*(11), 1746-1754.
19. Kalbasi, A., June, C. H., Haas, N., & Vapiwala, N. (2013). Radiation and immunotherapy: a synergistic combination. *The Journal of clinical investigation*, *123*(7), 2756-2763.
20. Kerenyi, N., Pandula, E., & Feuer, G. (1990). Oncostatic effects of the pineal gland. *Drug Metabolism and Drug Interactions*, *8*(3-4), 313-319.
21. Laamiri, F. Z., Bouayad, A., Hasswane, N., Ahid, S., Mrabet, M., & Amina, B. (2015). Risk Factors for Breast Cancer of Different Age Groups: Moroccan Data? *Open Journal of Obstetrics and Gynecology*, *5*(02), 79.
22. Lauby-Secretan, B., Scoccianti, C., Loomis, D., Benbrahim-Tallaa, L., Bouvard, V., Bianchini, F., & Straif, K. (2015). Breast-cancer screening—viewpoint of the IARC Working Group. *New England journal of medicine*, *372*(24), 2353-2358.
23. Li, J., Seibold, P., Chang-Claude, J., Flesch-Janys, D., Liu, J., Czene, K., Humphreys, K., & Hall, P. (2011). Coffee consumption modifies risk of estrogen-receptor negative breast cancer. *Breast Cancer Research*, *13*(3), 1-10.
24. Liu, Y., Zhou, Y., Huang, K.-H., Li, Y., Fang, X., An, L., Wang, F., Chen, Q., Zhang, Y., & Shi, A. (2019). EGFR-specific CAR-T cells trigger cell lysis in EGFR-positive TNBC. *Aging (Albany NY)*, *11*(23), 11054.
25. Ma, H., Bernstein, L., Pike, M. C., & Ursin, G. (2006). Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. *Breast Cancer Research*, *8*(4), 1-11.
26. MacLean, G. D., Reddish, M., Koganty, R. R., Wong, T., Gandhi, S., Smolenski, M., Samuel, J., Nabholtz, J. M., & Longenecker, B. M. (1993). Immunization of breast cancer patients using a synthetic sialyl-Tn glycoconjugate plus Detox adjuvant. *Cancer Immunology, Immunotherapy*, *36*(4), 215-222.
27. Melero, I., Gaudernack, G., Gerritsen, W., Huber, C., Parmiani, G., Scholl, S., Thatcher, N., Wagstaff, J., Zielinski, C., &

Faulkner, I. (2014). Therapeutic vaccines for cancer: an overview of clinical trials. *Nature reviews Clinical oncology*, *11*(9), 509-524.

28. Meric-Bernstam, F., Larkin, J., Tabernero, J., & Bonini, C. (2021). Enhancing anti-tumour efficacy with immunotherapy combinations. *The Lancet*, *397*(10278), 1010-1022.
29. Metcalfe, K., Finch, A., Poll, A., Horsman, D., Kim-Sing, C., Scott, J., Royer, R., Sun, P., & Narod, S. (2009). Breast cancer risks in women with a family history of breast or ovarian cancer who have tested negative for a BRCA1 or BRCA2 mutation. *British journal of cancer*, *100*(2), 421-425.
30. Morita, S., Oka, Y., Tsuboi, A., Kawakami, M., Maruno, M., Izumoto, S., Osaki, T., Taguchi, T., Ueda, T., & Myoui, A. (2006). A phase I/II trial of a WT1 (Wilms' tumor gene) peptide vaccine in patients with solid malignancy: safety assessment based on the phase I data. *Japanese journal of clinical oncology*, *36*(4), 231-236.
31. Nelson, H. D., Fu, R., Cantor, A., Pappas, M., Daeges, M., & Humphrey, L. (2016). Effectiveness of breast cancer screening: systematic review and meta-analysis to update the 2009 US Preventive Services Task Force recommendation. *Annals of internal medicine*, *164*(4), 244-255.
32. Nelson, H. D., Pappas, M., Cantor, A., Griffin, J., Daeges, M., & Humphrey, L. (2016). Harms of breast cancer screening: systematic review to update the 2009 US Preventive Services Task Force recommendation. *Annals of internal medicine*, *164*(4), 256-267.
33. Ngwa, W., Irabor, O. C., Schoenfeld, J. D., Hesser, J., Demaria, S., & Formenti, S. C. (2018). Using immunotherapy to boost the abscopal effect. *Nature Reviews Cancer*, *18*(5), 313-322.
34. Oh, J. K., Sandin, S., Ström, P., Löf, M., Adami, H. O., & Weiderpass, E. (2015). Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden. *International journal of cancer*, *137*(8), 1979-1989.
35. Page, D. B., Naidoo, J., & McArthur, H. L. (2014). Emerging immunotherapy strategies in breast cancer. *Immunotherapy*, *6*(2), 195-209.
36. Palmer, J. R., Wise, L. A., Horton, N. J., Adams-Campbell, L. L., & Rosenberg, L. (2003). Dual effect of parity on breast cancer risk in African-American women. *Journal of the National Cancer Institute*, *95*(6), 478-483.
37. Parkhurst, M. R., Riley, J. P., Igarashi, T., Li, Y., Robbins, P. F., & Rosenberg, S. A. (2004). Immunization of patients with the hTERT: 540-548 peptide induces peptide-reactive T lymphocytes that do not recognize tumors endogenously expressing telomerase. *Clinical Cancer Research*, *10*(14), 4688-4698.
38. Ross, R. K., Paganini-Hill, A., Wan, P. C., & Pike, M. C. (2000). Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *Journal of the National Cancer Institute,* 92(4), 328-332.
39. Rudqvist, N.-P., Pilones, K. A., Lhuillier, C., Wennerberg, E., Sidhom, J.-W., Emerson, R. O., Robins, H. S., Schneck, J., Formenti, S. C., & Demaria, S. (2018). Radiotherapy and CTLA-4 blockade shape the TCR repertoire of tumor-infiltrating T cells. *Cancer immunology research*, *6*(2), 139-150.
40. Santa-Maria, C. A., & Nanda, R. (2018). Immune checkpoint inhibitor therapy in breast cancer. *Journal of the National Comprehensive Cancer Network*, *16*(10), 1259-1268.
41. Saslow, D., Boetes, C., Burke, W., Harms, S., Leach, M. O., Lehman, C. D., Morris, E., Pisano, E., Schnall, M., & Sener, S. (2007). American Cancer Society guidelines for

breast screening with MRI as an adjunct to mammography. *CA: A cancer journal for clinicians*, *57*(2), 75-89.
42. Sinn, B., Von Minckwitz, G., Denkert, C., Eidtmann, H., Darb-Esfahani, S., Tesch, H., Kronenwett, R., Hoffmann, G., Belau, A., & Thommsen, C. (2013). Evaluation of Mucin-1 protein and mRNA expression as prognostic and predictive markers after neoadjuvant chemotherapy for breast cancer. *Annals of oncology*, *24*(9), 2316-2324.
43. Sugie, T. (2018). Immunotherapy for metastatic breast cancer. *Chin Clin Oncol*, *7*(3), 28.
44. Tan, S., Li, D., & Zhu, X. (2020). Cancer immunotherapy: Pros, cons and beyond. *Biomedicine & Pharmacotherapy*, 124, 109821.
45. Theurillat, J. P., Ingold, F., Frei, C., Zippelius, A., Varga, Z., Seifert, B., Chen, Y. T., Jäger, D., Knuth, A., & Moch, H. (2007). NY-ESO-1 protein expression in primary breast carcinoma and metastases—correlation with CD8+ T-cell and CD79a+ plasmacytic/B-cell infiltration. *International journal of cancer*, *120*(11), 2411-2417.
46. Thompson, J. A., Grunert, F., & Zimmermann, W. (1991). Carcinoembryonic antigen gene family: molecular biology and clinical perspectives. *Journal of clinical laboratory analysis*, *5*(5), 344-366.
47. Victor, T.-S., Rech, A. J., Maity, A., Rengan, R., Pauken, K. E., Stelekati, E., Benci, J. L., Xu, B., Dada, H., & Odorizzi, P. M. (2015). Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature*, *520*(7547), 373-377.
48. Yaghjyan, L., Rich, S., Mao, L., Mai, V., & Egan, K. M. (2018). Interactions of coffee consumption and postmenopausal hormone use in relation to breast cancer risk in UK Biobank. *Cancer Causes & Control*, 29(6), 519-525.
49. Cancer, C. G. o. H. F. i. B. (1997). Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *The Lancet*, 350(9084), 1047-1059.
50. Tiriveedhi, V., Fleming, T. P., Goedegebuure, P. S., Naughton, M., Ma, C., Lockhart, C., Gao, F., Gillanders, W. E., & Mohanakumar, T. (2013). Mammaglobin-A cDNA vaccination of breast cancer patients induces antigen-specific cytotoxic CD4+ ICOShi T cells. *Breast cancer research and treatment*, 138(1), 109-118.