Introduction

“Mind the gap” is as an audible or visual warning phrase to subway passengers in London of the significant space between the train door and station platform. We utilized this phrase to caution people to be mindful of the significant gap in knowledge about COVID-19 treatment and Cancer Immunotherapy. From the end 2019, a novel coronavirus causing respiratory-related disease known as COVID-19 has spreading rapidly among the whole world. The number of infected persons increasing rapidly worldwide and still continuing. Since the scientific knowledge gained from research on our body immune system and its reaction against foreign particles, it might be helpful to make prevention of future outbreaks. The urgent need to develop a vaccine to prevent SARS-CoV-2 pandemic is now the main focus all over the world. Over the past decade, scientists and drug industries have been works on different kinds of human threatening disease like H1N1 influenza, Ebola, Zika, SARS-CoV, MERS, etc. The knowledge to work in this area, helping the researcher a lot to develop a vaccine in at Pandemic Speed. However, the development of a new drug and starting application on human heal is a time-consuming manner. It becomes very hard in the case of COVID-19 as the virus characters changing rapidly. Here we discuss whether the anti-cancer immunotherapy could give some hope to protect against COVID-19 and also enrollment of cancer vaccine which started a randomized clinical trial to boost the treatment strategies against COVID-19 on an emergency basis.

Abstract

The urgent need to develop a vaccine to prevent SARS-CoV-2 pandemic is now the main focus all over the world. Over the past decade, scientists and drug industries have been works on different kinds of human threatening disease like H1N1 influenza, Ebola, Zika, SARS-CoV, MERS, etc. The knowledge to work in this area, helping the researcher a lot to develop a vaccine in at Pandemic Speed. However, the development of a new drug and starting application on human heal is a time-consuming manner. It becomes very hard in the case of COVID-19 as the virus characters changing rapidly. Here we discuss whether the anti-cancer immunotherapy could give some hope to protect against COVID-19 and also enrollment of cancer vaccine which started a randomized clinical trial to boost the treatment strategies against COVID-19 on an emergency basis.

Keywords: COVID-19- immunotherapy- Cancer- Cancer Vaccine

Viral vaccines that using to treat Cancer

Seasonal influenza virus infection is the most common viral infection by which people suffer every year. The Centers for Disease Control and Prevention
Cancer Treatment

early-stage bladder cancer approved for prostate cancer

Researcher start to use Influenza vaccines combined with therapies are current frontline therapies for cancer, its need more clinical trial outcome. Since, combination flu shots to treat cancer but to start application largely and have already proved its safe, so research start to use flu vaccine into the skin melanoma caused the tumors grow slower [7] by increasing immune-stimulating dendritic cells in the tumor, resulting an increase in CD8+ T-cells, which recognize and kill cancer cells. Human dendritic cells (DCs) play a crucial role in the immunity during vaccination against influenza. It was well known that Influenza vaccines trigger immunity through induce an IFN response in DCs, which help to increase the vaccine efficiency [8]. There is evidence of clinical trial [9] which proves dendritic cells vaccine (DCV) has minimal toxicity in patients with metastatic melanoma and its gives long time survival benefit. In this regard there is a major question arise that, can a Flu Shot be use full to treat Cancer? According to a publication in Proceedings of the National Academy of Sciences (PNAS), the patients receiving seasonal influenza vaccination may experience multiple clinical benefits like cancer immunotherapy. In a mouse model study, virus-specific memory T cells shows an alarming effect to reduce the tumor growth not only in lung tumour but also in metastatic triple-negative breast cancer [10]. Recently a study published where it was shows that flu vaccine is safe and dose not exacerbates immune events in cancer patients treated with immune checkpoint inhibitors (ICIs). However another study that contain 162 patients, showing no impact in response to flu vaccines in patients receiving checkpoint inhibitors [11]. Since the flu shots has been used by millions of people and have already proved its safe, so research start to use flu shots to treat cancer but to start application largely its need more clinical trial outcome. Since, combination therapies are current frontline therapies for cancer, researcher start to use Influenza vaccines combined with cancer immunotherapy.

There are several targets of vaccine that is under evaluation in clinical trials which are-CEA, Cytomegalovirus (CMV)-related antigens: foreign viral proteins expressed by CMV-infected cancer cells; Folate-related proteins; EGFR; HER2; Human Papilloma Virus (HPV)-related antigens; MAGE antigens; Mesothelin; MUC-1; NY-ESO-1; P53; PAP and PSA, Personalized neoantigens; Ras; Survivin; WT1. Most significant FDA-approved vaccines that are used for cancer immunotherapy are listed in Table 1 [12]. In their article describe in detail about therapeutic cancer vaccine and its future platform. Future directions are needed to involve the viral-based vaccines to treat patients regards adjuvant and neo-adjuvant settings and in combination with immunotherapy. An appropriate clinical endpoint is needed for therapeutic vaccines which will define the main strategies for the combination immunotherapy for cancer treatment.

Cancer vaccine to Treat Covid-19

Since SARS-CoV-2 coronavirus that causes the respiratory-related disease known as COVID-19 has spread widowed manner, researchers are working on preventive vaccines in an urgent basis. Based on the results of annual flu vaccines immunotherapy, researchers believe that these medicines may lead the immune system to act aggressively against COVID-19. According to a retrospective study from New York city cancer patients receiving immunotherapy were at increased risk for severe outcomes from COVID-19 [13]. But on the other hand study find that cancer immunotherapy does not increase risk for melanoma patients [14]. Now researchers discovered that cancer immunotherapy tolls can be use for COVID-19 treatment. They identified the right protein sequence target which used for cancer therapy also use for COVID-19 prevention [15]. Many research and clinical trial is going on optimizing designed vaccine which can maximizing the immune response and disease exacerbation. The main target is to produce vaccine that are safe and effective. Some of the important Cancer immune therapy drug that is under Clinical trials worldwide, are mentioned in Table 2. Now a day’s Chimeric antigen receptor (CAR) T-cell therapy is very promising immune therapy which use in cancer treatment [16]. Cytokine release syndrome (CRS) is an overwhelming and potentially life-threatening inflammatory response often seen in cancer patients. The CRS like symptoms

| Vaccine name                  | Cancer Treatment                                                                 |
|-------------------------------|----------------------------------------------------------------------------------|
| Cervarix®                     | HPV-related anal, cervical, head and neck, penile, vulvar, and vaginal cancers   |
| Gardasil®                     |                                                                                  |
| Gardasil-9®                   |                                                                                  |
| Hepatitis B (HBV) vaccine (HEPLISAV-B®) | can help prevent the development of HBV-related liver cancer                   |
| Bacillus Calmette-Guérin (BCG)| early-stage bladder cancer                                                      |
| Sipuleucel-T (Provenge®)      | approved for prostate cancer                                                    |
Famotidine is a histamine-2 receptor antagonist, widely available. It is used for the treatment of autoimmune disorders, including Crohn's disease and rheumatoid arthritis.

Lefflunomide is an inhibitor of dihydroorotate dehydrogenase (DHODH). It belongs to a class of drugs called disease-modifying antirheumatic drugs (DMARDs).

Hydroxychloroquine is an Autophagy inhibitor, when given in combination with cytotoxic agents have been found to suppress tumour growth and trigger cell death to a greater extent than chemotherapy alone, both in vitro and in vivo.

Enoxaparin is an anticoagulant (blood thinner) used to prevent blood clots that are sometimes called deep vein thrombosis (DVT), which can lead to blood clots in the lungs.
| Drug Name  | Mode of Action                                                                 | Used for Cancer Therapy                                                                 | Progress in COVID trial | Reference | Country                        |
|-----------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------|-----------|---------------------------------|
| Tocilizumab | Tocilizumab is a Humanized Monoclonal Antibody Against the Human Interleukin-6 (IL-6) Receptor. | 1. Phase I Trial of Trastuzumab and Pertuzumab in Combination With Tocilizumab in Metastatic HER2 Positive Breast Cancer.  
2. Phase II trial of Combination of Chemotherapy With Tocilizumab and Peg-IFN in Patients With Recurrent Ovarian Cancer.  
3. Phase II trial of Ipilimumab, Nivolumab, Tocilizumab and Radiation in Pretreated Patients With Advanced Pancreatic Cancer.  
4. Phase II study of Atezolizumab With Tocilizumab in Prostate Cancer.  
5. Phase II study of Nab-Paclitaxel and Gemcitabine With or Without Tocilizumab in Pancreatic Cancer.  
6. Phase II study of Tocilizumab in Hospitalized Cancer Patients With SARS-CoV-2. | Phase III NCT04412772 | Queen's Medical Center Honolulu, Hawaii, United States |
| Ulinastatin | Ulinastatin (or urinary trypsinogen inhibitor) is a serine protease inhibitor derived from human urine, with potential protective, anti-fibrinolytic and anticoagulant activities. | 1. A Prospective Randomized Trial Comparing Ulinastatin's Protection in Hepatocellular Carcinoma(HCC) Patients/Postoperative Hepatic Failure.  
2. Phase III trial of Ulinastatin for Reducing Radiation-Induced Oral Mucositis in Nasopharyngeal Carcinoma Patients | Phase I NCT04393311 | Stanford University Stanford, California, United States |
| Imatinib | Imatinib is a tyrosine kinase inhibitor that has been approved for treatment of many hematologic and solid neoplasm. | 1. Phase II Trial of Docetaxel Plus Imatinib Mesylate in Metastatic Breast Cancer  
2. Phase II Trial Of Imatinib Mesylate In Combination With Capecitabine In Metastatic Breast Cancer  
3. Phase II Trial Imatinib Mesylate in Combination With Docetaxel for the Treatment of Ovarian Cancer and Primary Peritoneal Carcinomatosis  
4. Phase I Study of Capecitabine, Cisplatin and Imatinib in Metastatic Gastric Cancer.  
5. Phase II Trial of Imatinib Mesylate Maintenance Therapy in Patients With Small Cell Lung Cancer.  
6. Phase II Study of Imatinib Mesylate and Gemcitabine for Advanced Pancreas Cancer | Phase III NCT04394416 | University of Maryland Medical Center Baltimore, Maryland, United States |
| N-acetylcysteine | NAC is the N-acetyl derivative of the naturally occurring amino acid, L-cysteine. It is a thiol-antioxidant. | 1. Phase I Study of Anti-oxidant Supplementation With N-Acetyl Cysteine in Breast Cancer  
2. Phase II study in Head and Neck Cancer patients undergoing Radiation Therapy | Phase II NCT04374461 | Memorial Sloan Kettering Cancer Center New York, New York, United States |
| Atovaquone | Atovaquone is an anti-protozoal drug that significantly reduces oxygen consumption in a variety of tumour cell lines | 1. Early Phase I Study in Non-small Cell Lung Carcinoma  
2. Early Phase I Study of Atovaquone With Conventional Chemotherapy for Acute Myeloid Leukemia (AML) | Phase II NCT04339426 | Honor Health Scottsdale, Arizona, United States |
| Telmisartan | It is an Angiotensin Receptor Blocker. | Retrospective Study of Angiotensin Receptor Blockers in neoplasm. Completed | Phase II NCT04360551 | University of Hawaii - Manoa, John A Burns School of Medicine UH Clinics at Kakaako Honolulu, Hawaii, United States |
Continued Table 2.

| Drug Name | Mode of Action | Used for Cancer Therapy | Progress in COVID trial | Reference | Country |
|-----------|----------------|-------------------------|-------------------------|-----------|---------|
| Tranexamic | TXA is a synthetic analog of lysine amino acid which reversibly binds four to five lysine receptor sites on plasmogen. | 1. Phase III study in bone cancer 2. Phase IV study in Surgery of Advanced Ovarian Cancer 3. Phase III study of Tranexamic Acid in Preventing Bleeding in Patients With Haematological Malignancies. 4. Phase IV stud in Colorectal Cancer Surgery 5. Phase III study in Head and Neck Neoplasms | Phase II | NCT04338074 | University of Alabama at Birmingham, Birmingham, Alabama, United States |
| Bicalutamide | It is an oral, non-steroidal, androgen receptor (AR) antagonist. | 1. A Phase II study in Metastatic Breast Cancer 2. Phase II RAD001 and Bicalutamide for Androgen Independent Prostate Cancer 3. Phase II Enzalutamide Versus Bicalutamide in Prostate Cancer 4. Phase III Study of Bicalutamide Versus Chemotherapy in AR Positive Metastatic Triple Negative Breast Cancer 5. Phase II Exemestane With or Without Bicalutamide in Stage IV Prostate Cancer | Phase II | NCT04374279 | Johns Hopkins Hospital, Baltimore, Maryland, United States |
| Sirolimus | Known as rapamycin, inhibitor of mTOR pathway | 1. Phase II Study of Rapamycin and Treantumab in Patients With HER-2 Receptor Positive Metastatic Breast Cancer 2. Phase II in Treating Patients With Advanced Pancreatic Cancer 3. Phase II Trial, Efficacy of Temsirolimus for Patients With Advanced Bladder Cancer | Phase II | Loyola University Medical Center, Chicago, Illinois, United States |
| Colchicine | Anti-inflammatory in nature and it can treat and prevent gout attacks. | 1. Phase II Evaluation the Palliative Effects of Colchicine on Primary Hepatic Malignant Tumors Unable to Receive Curative Treatment | Phase II | NCT04355143 | Cincinatti, Ohio, United States |

also found in COVID-19 patients [17]. Tocilizumab is the drug of choice to treat CRS, where the customized monoclonal antibody targeting the IL-6 receptor. This drug is under Phase III trial I to treat COVID-19. Another drug, CD24Fc also started to use as immunomodulator to treat COVID-19 [https://www.clinicaltrials.gov/ct2/show/NCT04317040]. Cell based therapeutic vaccine like aAPC Vaccine [https://clinicaltrials.gov/ct2/show/NCT04299724] where the artificial dendritic cells is to be use to activate and stimulate T cell proliferation. Lopinavir-Ritonavir a well-known and established drug used for different cancer treatment [18-19]. As a very well-known antiviral drug, Lopinavir-Ritonavir was widely used for laboratory research to treat SARS-Cov-2 prevention. According to a study based on 199 patients, this drug does not contain any significant effect to clinical improvement and reduce mortality in COVID-19 patients. On 4th July, 2020 WHO circulated a recommendation to discontinue the use of Lopinavir-Ritonavir after analysis the Solidarity trial interim results [20]. Considering all of this we need to wait until the completion of clinical trial to get new class of emerging therapy is aimed to prevent COVID-19.

In conclusions, COVID-19 pandemic giver very short time to find a proper therapeutic challenge. However, in global emergency, investigations progress rapidly and now phase III trials of new medications already started. As the whole process to approve a new drug which safe and effective, is time consuming. So, several drugs have been re-considered to treat COVID-19 which have been used in cancer therapy. This review considered the cancer immunotherapeutic agents that are potentially suitable drugs consider to treat COVID-19 to accelerate the process. This pandemic generated a endless demand for vaccine all over the world. We should continuing the clinical trial and developing most promising vaccine which can help us not only protect from the current pandemic also help us to gather much knowledge and fill our gaps to protect from future outbreak.

References

1. Sedighi M, Zahedi Bialvaei A, Hamblin MR, Ohadi E, Asadi A, Halajzadeh M, Lohrasbi V, Mohammadzadeh N, Amiriani T, Krutova M, Amini A, Kouhsari E. Therapeutic bacteria to combat cancer; current advances, challenges, and opportunities. Cancer Medicine. 2019 04 05.; https://doi.org/10.1002/cam4.2148
2. Vandeven N, Nghiem P. Pathogen-Driven Cancers and Emerging Immune Therapeutic Strategies. Cancer Immunology Research. 2014 01 01;2(1):9-14. https://doi.org/10.1158/2326-6066.cir-13-0179
3. Centers for Disease Control and Prevention (CDC) 11 April
2017. Overview of influenza surveillance in the United States. Available at: https://www.cdc.gov/flu/weekly/overview.htm. Accessed.
4. WebMD. (20 April 2017). What are your odds of getting the flu? Available at: http://www.webmd.com/cold-and-flu/flu-statistics.
5. National Foundation for Infectious Diseases. (7 July 2017). Understanding influenza. Available at: http://www.nfid.org/newsroom/news-conferences/2015-news-conferences/2015-news-conference/understanding-influenza.pdf.
6. Jayasundara K, Soobiah C, Thommes E, Tricco AC, Chit A. Natural attack rate of influenza in unvaccinated children and adults: a meta-regression analysis. BMC Infectious Diseases. 2014 Dec;14(1). https://doi.org/10.1186/s12879-014-0670-5
7. Palucka AK, Dhodapkar MV, Paczesny S, Burkeholder S, Witkowski KM, Steinman RM, Fay J, Banchereau J. Single Injection of CD34+ Progenitor-Derived Dendritic Cell Vaccine Can Lead to Induction of T-Cell Immunity in Patients With Stage IV Melanoma. Journal of Immunotherapy. 2003 09;26(5):432-439. https://doi.org/10.1097/00002371-200309000-00006
8. Athale S, Banchereau R, Thompson-Snipes L, Wang Y, Palucka K, Pascual V, Banchereau J. Influenza viruses differentially regulate the interferon response in human dendritic cell subsets. Science Translational Medicine. 2017 03 22;9(382):eaaf9194. https://doi.org/10.1126/scitranslmed.aaf9194
9. Dillman RO, Cornerth AN, Nistor GI, McClay EF, Amatruda TT, Depriest C. Randomized phase II trial of autologous dendritic cell vaccines versus autologous tumor cell vaccines in metastatic melanoma: 5-year follow up and additional analyses. Journal for ImmunoTherapy of Cancer. 2018 03 06;6(1). https://doi.org/10.1186/s40425-018-0330-1
10. Newman JH, Chessor CB, Herzog NL, Bommarredy PK, Aspromonte SM, Pepe R, Estupinian R, Aboelatta MM, Buddhadev S, Tarabichi S, Lee M, Li S, Medina DJ, Giurini EF, Gupta KH, Guevara-Aleman G, Rossi M, Nowicki C, Abed A, Goldufsky JW, Broucek JR, Redondo RE, Rotter D, Jhawar SR, Wang S, Kohlhapp FJ, Kaufman HL, Thomas PG, Gupta V, Kuzel TM, Reiser J, Paras J, Kane MP, Singer EA, Malhotra J, Denzin LK, Sant’Angelo DB, Rabson AB, Lee LY, Lasfar A, Langenfeld J, Schenkel JM, Figueroa CJ, Glickman MS, Joanow A, Kaltzas A, Lee YJ, Lucca A, Mariano A, Morjaria S, Nawar T, Papanicolaou GA, Predmore J, Redelman-Sidi G, Schmidt E, Seo SK, Sepkowitz K, Shah MK, Wolchok JD, Hohl TM, Taur Y, Kamboj M. Determinants of COVID-19 disease severity in patients with cancer. Nature Medicine. 2020 06 24,. https://doi.org/10.1038/s41591-020-0979-0
11. Failing JJ, Ho TP, Yadav S, Majithia N, Riaz IB, Shin JY, Schenk EL, Xie H. Safety of Influenza Vaccine in Patients With Cancer Receiving Pembrolizumab. JCO Oncology Practice. 2020 07;16(7):e573-e580. https://doi.org/10.1200/jop.19.00495
12. Guo C, Manjili M, Subjeck J, et al. Therapeutic cancer vaccines: past, present, and future. . Adv Cancer Res. 2013;119:421-75. https://doi.org/10.1016/B978-0-12-407190-2.00007-1
13. Robiotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, Bogler Y, Caldararo M, Figueroa CJ, Glickman MS, Joanow A, Kaltzas A, Lee YJ, Lucca A, Mariano A, Morjaria S, Nawar T, Papanicolaou GA, Predmore J, Redelman-Sidi G, Schmidt E, Seo SK, Sepkowitz K, Shah MK, Wolchok JD, Hohl TM, Taur Y, Kamboj M. Determinants of COVID-19 disease severity in patients with cancer. Nature Medicine. 2020 06 24,. https://doi.org/10.1038/s41591-020-0979-0
14. Gonzalez-Cao, Maria, et al. “Cancer immunotherapy does not increase the risk of death by COVID-19 in melanoma patients.” . medRxiv. 2020,. https://doi.org/10.1101/2020.05.19.20106971
15. Yarmarkovich M, Warrington JM, Farrel A, Maris JM. Identification of SARS-CoV-2 Vaccine Epitopes Predicted to Induce Long-Term Population-Scale Immunity. Cell Reports Medicine. 2020 06;1(3):100036. https://doi.org/10.1016/j.crm.2020.100036
16. Wang Z, Wu Z, Liu Y, Han W. New development in CAR-T cell therapy. Journal of Hematology & Oncology. 2017 02 21;10(1). https://doi.org/10.1186/s13045-017-0423-1
17. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020 03;395(10229):1033-1034. https://doi.org/10.1016/s0140-6736(20)30628-0
18. Sato A, Asano T, Okubo K, Isono M, Asano T. Nelfinavir and Ritonavir Kill Bladder Cancer Cells Synergistically by Inducing Endoplasmic Reticulum Stress. Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics. 2018 03 05;26(2):323-332. https://doi.org/10.3727/096504117x14957929842972
19. Okubo K, Isono M, Asano T, Sato A. Panobinostat and Nelfinavir Inhibit Renal Cancer Growth by Inducing Endoplasmic Reticulum Stress. Anticancer Research. 2018 Oct;38(10):5615-5626. https://doi.org/10.21873/2018.Anticancer.12896
20. World health Organization (WHO)- 4th July, 2020. https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-COVID-19.

This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License.