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Short Communication

Cancer Immunotherapy and COVID-19: Mind the Gap

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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.

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 immunotherapy and research specially help to understand the mechanism of action of virus and other foreign particle in human body and its prevention. On the other hand, cancer immunotherapy is now rapidly growing because of its mechanism is more target specific than chemotherapy or radiation treatment. Moreover, the immunotherapy has less side effects that chemotherapy and radiation commonly have i.e. damage healthy cells, commonly leading to hair loss. The main concern now a days whether anti-cancer immunotherapy can be used to treat COVID-19 or not? Basically, immunotherapy works on specific cancer immune system not all over the immune system. Sometimes immunotherapy leads to side effects due to its general immune system activation. Currently some immunotherapy used live pathogen to treat cancer [1-2] but these treatments only shown impact on a limited number of patients and cancer types. So, it is important to understand the fundamental differences between cancer immunotherapy and Immunotherapy to treat COVID-19 for the prevention of pandemic. There is an urgent need where Immuno-Oncology can help to make strategies to treat COVID-19. In this review we present a comprehensive analysis of available information on the drugs which used to treat cancer that can also being use for COVID-19 treatment to shortened the time length during the current outbreak.

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 (CDC) mention that, the patients admitted hospital with respiratory illness most of them suffer from influenza-like illness [3].

As per the report, in USA approximately 5%–20% of people infected by influenza virus in each season [4-5]. As per CDC 2019-2020 estimation (www.cdc.gov) 740000 was hospitalized due to flu where near about 64000 died due to this virus [6]. In their article mentioned many other counties estimation on influenza vaccine. To prevent the seasonal flu there is a huge demand in FDA-approved seasonal flu shots. Research is now focus to understand how immune responses against pathogens like influenza and their components could improve our much weaker immune response against some tumor. However, there are many factors involve in live infections, which done not found in tumors. It was found that, direct injection of 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].

Vaccine name	Cancer Treatment
Cervarix®	
Gardasil®	HPV-related anal, cervical, head and neck, penile, vulvar, and vaginal cancers
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

Table 1: FDA-approved Vaccines for the Treatment of Cancer.

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.

Drug Name	Mode of Action	Used for Cancer Therapy	Progress in COVIDtrial	Reference	Country
Infliximab	TNFα inhibitors currently FDA-approved for the treatment of autoimmune disorders, including Crohn's disease and rheumatoid arthritis	Terminated: Breast Cancer	Phase II	NCT04425538	Tufts Medical Center Boston, Massachusetts, United States
FT516	It is an off-the-shelf cryopreserved NK cell product derived from an iPSC that was transduced with a high affinity, ADAM17 non-cleavable CD16 (Fc receptor) that maintains CD16 on the cell surface, which remains fully functional after NK cell activation.	As monotherapy in acute myeloid leukemia (AML) and in combination with CD20 directed monoclonal antibodies in B-cell lymphoma.	Phase I	NCT04363346	University of Minnesota Minneapolis, Minnesota, United States
Pamrevlumab	Pamrevlumab is a first-in-class antibody that inhibits the activity of connective tissue growth factor (CTGF), a common factor in chronic fibrotic and proliferative disorders, characterized by persistent and excessive fibrous tissue which can lead to organ dysfunction and failure, and in cancer, characterized by promotion of tumor growth.	In Phase III clinical trial of Pamrevlumab in Combination With Gemcitabine Plus Nab-paclitaxel (G/NP) as Neoadjuvant Treatment in Patients With Locally Advanced, Unresectable Pancreatic Cancer	Phase II	NCT04432298	Research Center Greensboro, North Carolina, United States

Losartan	Losartan is an angiotensin II receptor blocker (ARB). It keeps blood vessels from narrowing, which lowers blood pressure and improves blood flow.	1. Phase I trial in Borderline Resectable or Locally Advanced Unresectable Pancreatic Cancer.2. Phase I trial with Sunitinib in Treatment of Osteosarcoma	Phase I	NCT04335123	University of Kansas Medical Center Kansas City, Kansas, United States
Tofacitinib	Tofacitinib is a JAK inhibitor. These drugs work by interfering with the inflammatory processes within the immune system that cause the symptoms of rheumatoid arthritis.	Phase I trial with LMB-100 in Neoplasms With Mesothelin Expression, Epithelioid Mesothelioma, Extrahepatic Cholangiocarcinoma, Pancreatic Adenocarcinoma	Phase II	NCT04412252	University Hospitals ClevelandMedical Center Cleveland,Ohio, United States
Famotidine	Famotidine is a histamine-2 receptor antagonist, widely available.	1. Phase I trial with XL281 is complete in solid tumors like Non-small-cell Lung Cancer,Colorectal Cancer Papillary Thyroid Cancer, Melanoma.2. Phase I trial with Savolitinib is complete in solid tumors.	Use in Non-hospitalized Patients With COVID-19	NCT04389567	Cold Spring HarborLaboratory Cold Spring Harbor, New York,United States
Leflunomide	Leflunomide, is an inhibitor of dihydroorotate dehydrogenase (DHODH).It belongs to a class of drugs calleddisease-modifying antirheumatic drugs (DMARDs).	1. Phase I/II Trial in Women With Previously Treated Metastatic Triple Negative Cancers.2. Phase II/III Study with Mitoxantrone/ Prednisone in Patients With Hormone-Refractory Prostate Cancer.3. Phase II study for Patients With Anaplastic Astrocytoma4. Phase III Randomized versus Procarbazine for Patients With Glioblastoma Multiforme.	Phase I	NCT04361214	University of Chicago Chicago, Illinois, United States
Hydroxychloroquine	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	1. Phase II in Previously Treated Patients With Metastatic Pancreatic Cancer.2. Phase I/II Study of Hydroxychloroquine and Itraconazole as Therapy for Prostate Cancer.3. Phase II study with Sorafenib in	Phase IV	NCT04382625	Kootenai Health Coeur d'Alene, Idaho, United States

	and in vivo.	Hepatocellular Cancer			
Enoxaparin	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.	1. Phase II study of Rosuvastatin and Enoxaparin in Ovarian Cancer.2. Phase II/III Trial Of Simultaneous Pancreatic Cancer Treatment With Enoxaparin and ChemoTherapy.3. Phase III Study of Standard Treatment with Enoxaparin in Small Cell Lung Cancer.4. Phase II Trial of Enoxaparin Thromboprophylaxis in Cancer Patients With Elevated Tissue Factor Bearing Microparticles.5. Phase III-b, Multi-centre,Open-label, Parallel Study of Enoxaparin With Chemotherapy in Patients with Gastric andGastro-oesophageal Cancer.	Phase III	NCT04359277	NYU Langone HealthNew York, New York, United States
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 I/II trial of Combination of Chemotherapy With Tocilizumab and Peg-Intron 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	Phase III	NCT04412772	Queen's Medical Center Honolulu, Hawaii,United States

		study of Tocilizumab in Hospitalized Cancer Patients With SARS-CoV-2.			
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) P atients'Postoperativ e 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 Cancer2. Phase II Trial Of Imatinib Mesylate In Combination With Capecitabine In Metastatic Breast Cancer3. Phase II Trial Imatinib Mesylate in Combination With Docetaxel for the Treatment of Ovarian Cancer and Primary Peritoneal Carcinomatosis4. 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 I/II Study of Imatinib Mesylate and Gemcitabine for Advanced Pancreas Cancer	Phase III	NCT04394416	University of Maryland Medical CenterBaltimore, 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 Cancer2. Phase II study in Head and Neck Cancer patients undergoing Radiation Therapy	Phase II	NCT04374461	Memorial Sloan Kettering Cancer CenterNew 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 Carcinoma2. 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.	RetrospectiveStudy 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
Tranexamic	TXA is a synthetic analog of lysine amino acid which reversibly binds four to five lysine receptor sites on plasminogen.	Phase III sudy in bone cancer 2 Phase IV study in Surgery of Advanced Ovarian Cancer3. Phase III study of Tranexamic Acid in Preventing Bleeding in Patients With Haematological Malignancies.4. Phase IV stud in Colorectal Cancer Surgery5. 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 Cancer3. Phase II Enzalutamide Versus Bicalutamide in Prostate Cancer4. Phase III Study ofBicalutamide Versus Chemotherapy in AR Positive Metastatic Triple Negative Breast Cancer5. 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 mTORpathway	1. Phase II Study of Rapamycin and Trastuzumab in Patients With HER-2 Receptor Positive Metastatic	Phase II		Loyola University Medical Center Chicago, Illinois, United States University of Cincinnati

		Breast Cancer2. Phase II in Treating Patients With Advanced Pancreatic Cancer3. Phase II Trial, Efficacy of Temsirolimus for Patients With Advanced Bladder Cancer			Cincinnati,Ohio, United States
Colchicine	Anti-inflammatory in nature and It can treat and prevent gout attacks.	Phase II Evaluation the Palliative Effects of Colchicine on Primary Hepatic Malignant Tumors Unable to Receive Curative Treatment	Phase II	NCT04355143	

Table 2: Cancer Immunotherapy Drug that Consider for COVID -19 Treatment.

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 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 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 dose 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.

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