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Research Article

Immunotherapy and Esophageal Cancer

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Abstract

Cancer of the esophagus is characterized as an aggressive disease with a poor outcome. A few drugs have showed to significantly benefit the overall survival and disease free survival of esophageal cancer patients, and many are currently under clinical investigations in the therapy of esophageal cancer. The two most common types of esophageal cancer are squamaous cell carcinoma and adenocarcinoma, according to the cell of origin and location. Little is known about the molecular pathogenesis of this tumor. Few genes, such as tumor suppressor genes, oncogene, and apoptotic genes, have been identified to have a function in its development. The existing modest results, with the conventional treatments in the management of esophageal carcinoma, generated a substantial interest in novel lines of attack, mainly immunotherapy. This chapter will highlight the different classes of immunotherapeutic agents explored in the therapy of esophageal carcinoma: Checkpoint Inhibitors, Vaccine based immunotherapy, Adoptive cell therapy, Monoclonal Antibodies, Adjuvant Immunotherapy, Cytokines, Kinase inhibitors, mammalian Target of Rapamycin inhibitors and proteasome inhibitors.

Keywords: *Esophageal cancer; Squamous cell carcinoma; Adenocarcinoma; Monoclonal antibodies; Immunotherapy*

Abbreviations: ATP : Adenosine triphosphate; ADC: Antibody-drug conjugate; ADCA: Adenocarcinoma; APC: Anaphase-promoting complex; APC: antigen-presenting cells; B7H1: B7 homolog 1; bcl-2: B-cell lymphoma -2; bcl-xl: B-cell lymphoma extra-large; BE: Barrett's esophagus; bi-shRNA: bifunctional short hairpin RNA; DC: dendritic cell; BMI: body mass index; CAR: chimeric antigen receptor; CTSB: Cathepsin B; CDK4: Cyclin-dependent kinase 4; CTLA 4: cytotoxic T-lymphocyte-associated antigen-4; DP: Dipeptidyl peptidase; ECRG4: Esophageal cancer related gene 4; E2F-1: E2 Transcription Factor -1; EGFR: epidermal growth factor receptor; ERK: extracellular signal-regulated kinase; FzE3: Frizzled gene in Human esophageal carcinoma cells 3; FRAT1: Frequently Rearranged In Advanced T-Cell Lymphomas 1; FEZ1: Fasciculation and Elongation protein Zeta 1; FKBp-12: immunophilin FK Binding Protein-12; FGFR: fibroblast growth factor receptor; FLT3: Fms-related tyrosine kinase 3; GERD: Gastro esophageal reflux disease; GASC1: Gene Amplified in Squamous Cell Carcinoma 1; HGFR :human hepatocyte growth factor receptor (or c-Met); HLA: human leukocyte antigen; HEGFR 2: human epidermal growth factor receptor 2; HPV: human papilloma virus; IgG1-interleukin-12; IL-2: interleukin-2; IgSF: immunoglobulin superfamily; IgG2: immunoglobulin G2; Int-2/hst-1: integrated – 2/heparin-binding secretory transforming-1; LAG-3: lymphocyte activation gene-3; LOH: loss of heterozygosity; MAGE-A3: melanoma antigen A3; MCC: Mutated In Colorectal Cancers; MHC: major histocompatibility complex; KIR: killer-cell immunoglobulin-like receptors; MDM-2: Mouse double minute 2; mTOR: mammalian Target of Rapamycin; MT: Metallothionein; NHS-IL-12: tumor necrosis-targeting human; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PBMC: peripheral blood mononuclear cell; NY-ESO-1: New York-esophageal cancer-1; ODC: Ornithine decarboxylase; PI3K: phosphatidylinositol 3-kinase; PBL: peripheral blood lymphocyte; PCNA: Proliferating cell nuclear antigen; PD-1: programmed death-1 or programmed cell death-1; PDGFR-beta: platelet-derived growth factor receptor beta subunit; TIL: tumor-infiltrating lymphocytes; TAA: tumor-associated

antigen; TCR: T-cell receptor; mAb: monoclonal antibodies; SN-38: 7-ethyl-10-hydroxycamptothecin; rhGM-CSF : recombinant human granulocyte macrophage-colony stimulating factor; TEM1: tumor endothelial marker; TACSTD2: umor-associated calcium signal transducer 2; TF: Tissue Factor; rhIL-15: recombinant human Interleukin IL-15; RAF: Rapidly Accelerated Fibrosarcoma kinase; MEK: mitogen-activated protein kinase; SCC: squamous cell carcinoma; RTK: receptor tyrosine kinase; RET: rearranged during transfection; TSG: tumor suppressor genes; US: United States; VEGFR2: vascular endothelial growth factor type 2 receptor; VEGF: vascular endothelial growth factor; WWOX: WW domain containing oxireductase

Introduction

Esophageal cancer is the sixth most common cause of cancer death worldwide [1]. It arises from the mucosa and grows outward through the submucosa in the direction of the muscularis propria and adventitia [2]. Esophageal cancer can be classified according to the two types of mucosal cell lining. Squamous cell carcinoma (SCC) occur throughout the length of the esophagus, or the adenocarcinoma (ADCA) which is confined to the area just above the gastro-esophageal junction [2].

Esophageal cancer constitutes about 1% of all cancers diagnosed in the US; however, it is much more common in other parts of the world, such as northern China, Iran, southern Africa, and India where the main type is SCC [2]. Although not common in the United States (US), it is estimated that about 16,910 new esophageal cancer cases will be diagnosed in 2016, of which 13,460 are men and 3,450 are women. Cancer of the esophagous is expected to be the cause of approximately 15,690 deaths (e.g., 12,720 in men and 2,970 in women) in 2016 [2]. It is 3 to 4 times more common among men than women with a lifetime risk about 1 in every 125 men and about 1 in every 435 women. Adenocarcinoma (ADCA) is the most common type of esophageal cancer among whites, while SCC is more common in Blacks [1].

Risk factors [2,3]

Esophageal cancer may develop due to the deoxyribonucleic acid (DNA) damage caused by the chronic irritation of esophageal mucosal cells. Factors, commonly linked to the increased risk of esophageal cancer are as follows:

Tobacco and Alcohol Use

Tobacco use increases the risk of both SCC and ADCA types of esophageal cancer. Alcohol ingestion, although not a pertinent risk factor, may increase the risk of SCC subtype. The combination of both, smoking and alcohol use, amplifies the risk of esophageal cancer especially the SCC type [2].

Obesity

Overweight, is a body mass index (BMI) between 25.0-29.9, and obesity, BMI ≥30, have been shown to increase the risk of esophageal cancer by approximately 2- to 3-fold in 2 metaanalysis specifically the ADCA type. Those who are obese have a higher risk than overweight people to develop esophageal cancer [4,5].

Diet

The excessive consumption of red or processed meat may increase he risk of esophageal cancer. Moreover, the frequent consumption of very hot beverages, it may irritate or weaken the esophageal cells increasing the risk of esophageal cancer [3].

Gastro esophageal reflux disease (GERD) and Barrett's esophagus (BE)

Barrett's Esophagus (BE) are complications of a long standing gastroesophageal reflux disease (GERD) where patients suffer from recurrent acidic gastric reflux up the esophagus. GERD increases the risk of esophageal ADCA 5 times more in patients who have an acidic reflux every week or more compared to patients who have less or none. BE patients are 11 times more at risk to develop ADCA of esophageal cancer when compared to the general population [3].

Achalasia

Patients with Achalasia, a neurogenic esophageal motility disorder, carries a high risk of esophageal cancer that lasting for approximately 15 years after its diagnosis [3].

Tylosis

Patients with Tylosis A, is a very rare genetic skin disorder with late onset of non-epidermolytic palmoplantar keratoderma (NEPPK) that affects those between the age of 5 and 15, placing them at a higher risk of developing SCC esophageal cancer. [3] On the other hand Tylosis B is a benign disorder, with an onset at the first year of life.

Plummer Vinson syndrome

Plummer-Vinson or Paterson-Kelly syndrome is a rare condition characterised by iron deficiency anemia and dysphagia. It is associated with increased risk of SCC of esophagus or pharynx [3].

Human Papilloma Virus (HPV)

Human papilloma virus (HPV) infection is a possible risk factor of SCC esophageal cancer. The HPV connection to esophageal cancer is only seen in parts of Asia and south Africa in about one-third of patients with the disease. This was not documented elsewhere in the western world [3].

Chemical exposure

Occupational hazards, such exposure to certain chemical fumes and solvents, have been implicated in the increased incidence of esophageal cancer among these workers [2].

Molecular Pathophysiology

Despite the advances in the molecular pathogenesis, it still unkown what are the precise genetic aberrations responsible for triggering and development of Esophageal Cancer. Some tumor related genes, such as tumor suppressor genes (TSG), oncogene, and apoptotic genes, are recognized for their role in the pathogenesis of Esophageal Carcinoma. These malfunctioning genes and their specific role in the cancer of the esophagus are discussed below (Figure 1):

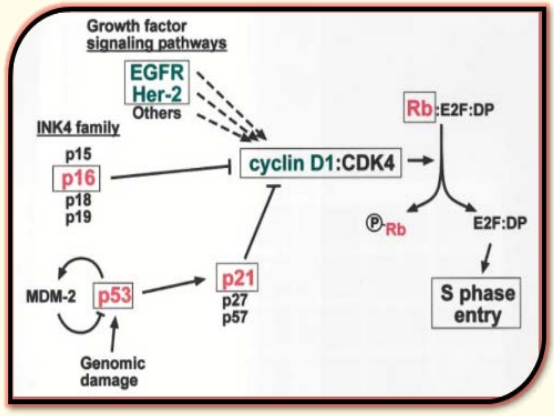

Figure 1: *Oncogenes found to be frequently up-regulated in esophageal malignancy are indicated in green; tumor-suppressor genes frequently inactivated are indicated in red.*

Adopted from Cancer of the Upper Gastrointestinal Tract, By Mitchell C. Posner, Everett E. Vokes, Ralph R. Weichselbaum, American Cancer Societ 2002.

Abb: EGFR: epidermal growth factor receptor. Her-2: human epidermal growth factor receptor 2. E2F-1: E2 Transcription Factor -1. DP: Dipeptidyl peptidase. CDK4: Cyclin-dependent kinase 4 . MDM-2: Mouse double minute 2.

Tumor suppressor genes

Tumor suppressor genes (TSG) are normal genes that can be inactivated by genetic or epigenetic changes, such as point mutations, deletions, loss of heterozygosity (LOH), promoter methylation, abnormal splicing, deregulation of imprinting and haplo insufficiency. LOH, which causes inactivation of most candidate TSG, have been found in the critical regions of chromosomes 1p, 3p, 4, 5q, 9, 11q, 13q, 17q, and 18q in Esopahgeal Carcinoma. Chromosome region 17q25.2–25.3 carries the autosomal dominant premalignant dermatologic condition, tylosis [6,7]. In almost all cases of Esophageal Cancer, LOH, involving the Anaphase-promoting complex (APC) and Mutated In Colorectal Cancers (MCC) genetic loci, is implicated in the development and/or progression of the disease [8].

In specifically Esophageal SCC, WWOX (WW domain containing oxireductase) which is a TSG [9], and mutations in codons 175, 248, and 273 of p53 gene may give an added pathway for its occurrence [10].

Oncogenes

Oncogenes can into cancer if they become activated (Osborne, Wilson and Tripathy, 2006). Cyclin D1, EGFR, Her-2, FRAT1, c-myc, c-ras, and Int-2/hst-1 are the most commonly upregulated oncogenes in esophageal cancer. They are instigated throught many different genetic aberrations, such as point mutations, amplification, rearrangement and over-expression. Amplification and overexpression are the most common existing types [10].

Apoptotic genes

The most frequently expressed apoptotic genes in esophageal carcinoma are: anti-apoptotic protein bcl-2 and bcl-xl [11], Proliferating cell nuclear antigen (PCNA) [12], Survivin [13], Matrix metalloproteinase-7[14], Metallothionein (MT)[15], Overexpression of E2F-1[16], DcR3/M68 [17], GASC1 [18], Cathepsin B (CTSB) [19], FEZ1 [20], Ornithine decarboxylase (ODC)[21], FzE3 [22] and Esophageal cancer related gene 4 (ECRG4) [23].

Immunotherapy

The current available drugs, FDA/ Non FDA approved or still under clinical trials, are categorized according to their mechanism of action into the following groups: checkpoint inhibitors/immune modulators, therapeutic vaccines, adoptive T cell transfer, monoclonal antibodies, adjuvant immunotherapies, cytokines, kinase inhibitors and mTOR inhibitors [24].

Checkpoint Inhibitors / Immune Modulators

Several checkpoint inhibitors, targeting multiple different checkpoints, are currently in development. Additional details related to the non Food and Drug Administration (FDA) approved check point inhibitors and immune modulators are presented in Table 1.

Drug	Clinical trial identifier no.	Phase	Study Design	Target
MEDI4736	NCT01693562	Phase I, Phase II	Non-Randomized, Safety/Efficacy Study, open label	PD-L1
MK-3475 Pembrolizumab	NCT02054806	Phase I	Efficacy Study, open label	PD-1

MPDL3280A	NCT01375842	Phase I	Non-Randomized, open label	PD-L1
MPDL3280A	NCT01633970	Phase I	Non-Randomized, Safety Study, open label	PD-L1
BMS-663513 Urelumab	NCT01471210	Phase I	Non-Randomized, Safety Study, open label	4-1BB/CD137
PF-05082566	NCT01307267	Phase I	Non-Randomized, Safety Study, open label	4-1BB/CD137
Lirilumab+ Nivolumab	NCT01714739	Phase I	Non-Randomized, Safety Study, open label	KIR PD-1
Ipilimumab + Imatinib Mesylate	NCT01738139	Phase I	Safety/Efficacy Study, open label	CTLA-4 c-Kit
BMS-986016 Nivolumab	NCT01968109	Phase I	Non-Randomized, Safety Study, open label	LAG-3 PD-1
PDR001	NCT02404441	Phase I/II	Non-Randomized, Safety Study, open label	PD-1
LAG525 +/- PDR001	NCT02460224	Phase I/II	Non-Randomized, Safety Study, open label	LAG-3 and PD-1

Table 1: *Non-FDA approved checkpoint inhibitors [25-35].*

Vaccine based immunotherapy

In esophageal cancer, several trials of vaccines, given alone or with other therapies, are currently enrolling patients. The non FDA approved vaccines are described in Table 2.

Vaccines	Clinical trial identifier no.	Phase	Study Design	Target
H1299 Lysate Vaccine	NCT02054104	Phase I, Phase II	Randomized, Efficacy Study, open label	Cytotoxic T Lymphocyte
DCVax-Direct	NCT01882946	Phase I, Phase II	Safety/Efficacy Study, open label	To reduce tumor growth
FANG	NCT01061840	Phase I	Non-Randomized, Safety Study, open label	Furin protein production
DEC-205-NY-ESO-1	NCT01522820	Phase I	Non-Randomized, Safety Study, open label	NY-ESO-1
Tumor cell vaccines	NCT01341496	Phase I	Safety Study, open label	Immune response
Tumor cell vaccines	NCT01258868	Phase I	Non-Randomized, Safety Study, open label	Immune response

Table 2: *Non-FDA approved Vaccines [36-41].*

Adoptive cell therapy

Another major opportunity of immunotherapy for esophageal cancer is adoptive T cell transfer. Several trials of adoptive T cell transfer techniques are currently underway for patients with esophageal cancer. A list of non-FDA approved adoptive T cell therapies are included in Table 3.

Drug	Clinical trial identifier no.	Phase	Study Design	Target
TIL	NCT01174121	Phase II	Non-Randomized, Safety/Efficacy Study, open label	Cell growth
Anti-NY ESO-1 mTCR PBL	NCT01967823	Phase II	Non-Randomized, Safety/Efficacy Study, open label	NY-ESO-1
Anti-MAGE-A3-DP4 TCR	NCT02111850	Phase I, Phase II	Non-Randomized, Safety/Efficacy Study, open label	MAGE-A3-DP4
Anti-VEGFR2 CAR CD8 plus PBL	NCT01218867	Phase I, Phase II	Non-Randomized, Safety/Efficacy Study, open label	VEGFR2

Table 3: *Non-FDA approved adoptive T cell therapy [42-45].*

Drug	Clinical trial identifier no.	Phase	Study Design	Target
Cetuximab	NCT00655876	Phase III	Randomized, double blind	EGFR
MM-111	NCT01774851	Phase II	Randomized, Efficacy Study, open label	HER2, HER3
Bevacizumab	NCT01212822	Phase II	Efficacy Study, open label	VEGF
IMMU-132	NCT01631552	Phase II, Phase I	Safety/Efficacy Study, open label	Trop-2
MORAb-004	NCT01748721	Phase I	Safety Study, open label	Endosialin/TEM1
OMP-52M51	NCT01778439	Phase I	Safety/Efficacy Study, open label	Tumor cells
ABT-700	NCT01472016	Phase I	Non-Randomized, Safety Study, open label	Tumor cells
MM-151	NCT01520389	Phase I	Non-Randomized, Safety Study, open label	EGFR
CEP-37250/KHK2804	NCT01447732	Phase I	Non-Randomized, Safety Study, open label	Glycolipids
Panitumumab	NCT01627379	Phase III	Randomized, Safety/Efficacy Study, open label	EGF
Nimotuzumab	NCT02034968	Phase II	Safety/Efficacy Study, open label	EGFR
HuMax-TF-ADC	NCT02001623	Phase I/II	Safety/Efficacy Study, open label	Tissue Factor

Table 4: *Non-FDA approved monoclonal antibodies [46-57].*

FDA Approved Therapies

Trastuzumab: A recombinant humanized monoclonal antibody directed against human epidermal growth factor receptor 2 (HER2). After binding to HER2 on the tumor cell surface, trastuzumab induces an antibody-dependent cell-mediated cytotoxicity against tumor cells that overexpress HER2. HER2 is overexpressed by many adenocarcinomas, particularly breast adenocarcinoma [58].

Ramucirumab: A recombinant, fully human monoclonal antibody directed vascular endothelial growth factor receptor 2 (VEGFR-2) with antiangiogenesis activity. Ramucirumab specifically binds to and inhibits VEGFR-2, which may result in an inhibition of tumor an-

giogenesis and a decrease in tumor nutrient supply. VEGFR-2 is a pro-angiogenic growth factor receptor tyrosine kinase expressed by endothelial cells [59].

Adjuvant Immunotherapy

Adjuvants are substances that are either used alone or combined with other immunotherapy to boost the immune response. Some adjuvant immunotherapeutic modalities use ligands-molecules that bind to proteins such as receptors to help control the immune response. These ligands can be either stimulating (agonists) or blocking (antagonists).

Non-FDA approved adjuvant therapy

A treatment that is given in addition to the primary, main or initial treatment. The Non-FDA approved adjuvant therapy is described in Table 5.

Drug	Clinical trial identifier no.	Phase	Study Design	Target
CBLB502	NCT01527136	Phase I	Safety study, open label	Stop tumor cells from growing

Table 5: *Non-FDA approved adjuvant immunotherapeutic drug [60].*

Cytokines

Cytokines are messenger molecules that help control the growth and activity of immune system cells. The Non-FDA approved cytokines are described in Table 6.

Drug	Clinical trial identifier no.	Phase	Study Design	Target
rh IL-15	NCT01572493	Phase I	Safety study, open label	Stimulate the immune system
NHS-IL-12	NCT01417546	Phase I	Safety study, open label	Cancer cells
Aldesleukin	NCT01697527	Phase II	Safety/Efficacy Study, open label	NY-ESO-1

Table 6: *Non-FDA approved cytokines [61-63].*

Kinase inhibitors

Kinase inhibitor is described as a type of enzyme that blocks the action of one or more inhibitors (Broekman, Giovannetti and Peters, 2011). Table 7, below, describes the non FDA approved kinase inhibitors.

Drug	Clinical trial identifier no.	Phase	Study Design	Target
Sorafenib	NCT00917462	Phase II	Safety/Efficacy Study, open label	VEGF
Sunitinib	NCT00702884	Phase II	Open label	VEGFR2, PDGFRb, c-kit
Afatinib	NCT01522768	Phase II	Safety/Efficacy Study, open label	RTK, EGFR
PF-00299804	NCT01608022	Phase II	Safety/Efficacy Study, open label	EGFR
BKM120 Burparlisib	NCT01806649	Phase II	Safety/Efficacy Study, open label	Class I PIK3
Regorafenib	NCT01913639	Phase II	Safety/Efficacy Study, open label	VEGFRs 2 and 3, and Ret, Kit, PDGFR and Raf kinases
Icotinib Hydrochloride	NCT01973725	Phase II	Safety/Efficacy Study, open label	EGFR

BYL719 and MEK162	NCT01449058	Phase I/II	Safety/Efficacy Study, open label	PI3K and MEK
LJM716 and BYL719	NCT01822613	Phase I/II	Safety/Efficacy Study, open label	PI3K and HER3
LY294068	NCT02530437	Phase I/II	Safety/Efficacy Study, open label	smoothened receptor antagonist
Neratinib	NCT01953926	Phase II	Safety/Efficacy Study, open label	HER2, HER3, EGFR
Nintedanib	NCT02234596	Phase II	Safety/Efficacy Study, open label	VEGFR, FGFR, PDGFR

Table 7: *Non-FDA approved kinase inhibitors [64-75].*

mTOR inhibitors

Mechanistic target of rapamycin (mTOR), a serine threonine protein kinase that controls cell growth, cell development, cell activity, cell progression, protein integration, autophagy, and imitation (Laplante and Sabatini, 2012). The Non FDA approved mTOR inhibitors are included in Table 8.

Drug	Clinical trial identifier no.	Phase	Study Design	Target
Everolimus	NCT00985192	Phase II	Open label	FKBP-12

Table 8: *Non-FDA approved mTOR inhibitor [76].*

proteasome inhibitor

Proteasome inhibitors are anticancer therapies that worki to regulate protein activities (Adams, 2003). The non FDA approved proteasome inhibitors are included in Table 9.

Drug	Clinical trial identifier no.	Phase	Study Design	Target
Carfilzomib With Irinotecan	NCT01941316	Phase I	Open label	FKBP-12

Table 9: *Non-FDA approved proteasome inhibitors [77].*

Conclusion

Esophageal cancer has one of the highest mortality rates and carries an inferior prognosis. The ability to improve the overall survival as well as the disease free survival of esophageal cancer patients is increasing, as our knowledge and understanding of functioning of the immune system is expanding. Many promising advances has been attained in the oncology application of immunotherapy in the last decade. However, recent activities have enhanced our comprehension of the tumor microenvironment, various immunotherapeutic modalities or combination therapies, such as chemotherapy and immunotherapy. Moreover, the effects of the numerous strategies in combination with immunotherapy in different types cancer are still in the exploratory phase. Experimental preclinical and clinical trials are needed to uncover the vast potential of immunotherapy in treating cancer patients. Despite the large number of agents under investigations, the goal of therapy in cancer of the esophagous has not yet been realized.

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