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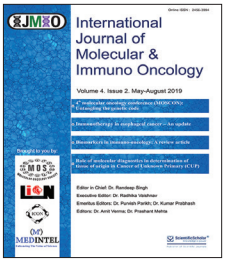

Review Article

Immunotherapy in esophageal cancer – An update

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ABSTRACT

Esophageal cancer continues to remain a global problem. The majority of patients with advanced and/or metastatic disease will have limited survival, which has essentially remained unchanged over the past 20 years. The dawn of the immunotherapy resurgence has brought hope in the lives of many patients with lung cancer and other solid tumors. The emerging data for esophageal cancer also indicates benefit in selected patients. We summarize the current data available in this review.

Keywords: Checkpoint inhibitors, Immune modulators, Peptide vaccines, Oncolytic viruses, Programmed death-ligand 1, Microsatellite instability, Adverse reactions

INTRODUCTION

Esophageal cancer is a significant problem globally. It ranks 7th in incidence and 6th in death rates among all cancers. In India, its position is similar, being 6th rank for incidence as well as death rate [Table 1].[1,2] In our country, its incidence is steadily increasing among women and marginally declining among men. The actual figures for 2010 and 2015 as well as the projected incidence for 2020 are shown in Table 2.[3] The discrepancy in the figures in Globocan data and Indian Cancer Atlas data is because Globocan policy is to use projections and estimation. This has been seen earlier for other cancers as well.

While the label of esophageal cancer refers to the organ of origin, a common anatomical site cases can be clearly demarcated into two distinct disease entities based on their epidemiology and pathology, namely squamous cell (SS) versus adenocarcinoma (AD). As far as Caucasians are concerned, in the 1960s, SC accounted for 90% of all cases. However, incidence of AD has steadily increased until it now forms 60% of all cases.[4-7]

In the USA, oral squamous cell carcinoma (SCC) incidence rates have fallen by 3.6% annually 1998–2003 and a similar fall of 3.3% occurred in the annual standardized incidence rate in China from 1989 to 2008; decreased incidence rates are also apparent in high incidence areas within China such as Cixian.[8,9]

In India (like several other low- and middle-income countries), SS still makes up 4/5th (80%) of esophageal cancer cases (related to tobacco and alcohol), although AD is on the increasing

trend, reflecting socioeconomic changes (reflux causing Barrett's esophagitis).[10] This is similar to the disparity in the incidence of esophageal AD among Whites versus Blacks in North America.[11]

Majority of our patients present in advanced stage. When such patients are treated with surgical resection with curative intent, a significant number develop recurrence and overall survival (OS) is <12 months. Hence, chemotherapy (CT) or chemoradiotherapy has become standard adjuvant therapy for such patients.[12,13]

Data of 453 patients with esophageal cancer from Tata Memorial Hospital showed age as an important prognostic factor. Patients who were 35 years or younger had a trend of having more advanced disease at initial presentation, lower chance of complete resection, higher risk of recurrence, and poorer disease-free survival (though not statistically significant). However, younger patients had lower risk of cardiopulmonary complications and post-operative deaths.[14]

There is an ongoing and rapidly evolving search for novel therapies tailored to the molecular composition of the tumor. Progress has been so significant that we now have a new molecular classification SS of esophagus being categorized into three distinct groups based on the primary molecular pathway affected by the genetic alterations [Table 3].[15]

Unfortunately, advanced esophageal cancer cases continue to have a poor outcome. This remained unchanged in spite of novel developments in systemic CT, combination regimen, as well as driver mutation-based targeted precision therapy.[16]

Hence, the focus has shifted to immunotherapy, the new ray of hope – with special interest in using microsatellite instability (MSI), programmed death-ligand 1 (PD-L1), and programmed cell death protein 1 (PD-1) to enrich population most likely to benefit.[17,18]

Table 1: Esophageal cancers – Globocan data, 2018 (published January 2019).

	India rates		World rates	
	Incidence	Deaths	Incidence	Death
Number	52,396	46,504	572,034	508,585
Rank	6th	6th	7th	6th
% of all cancers	5.04%	6.51%	3.2%	5.3%

Table 2: Esophageal cancers in India (C15).

	Males	Females	Total
2010	23,280	18,417	41,697
2015	22,114	20,070	42,184
2020	20,642	21,871	42,513

Table 3: Molecular classification of esophageal SCCs.

Group	Metabolic pathway involved
1	NRF2 pathway
2	NOTCH1, PTEN, PIK3R1, KDM6A, KDM2D, ZNF750, and/or CDK6 related pathways
3	Phosphoinositide 3-kinase (PI3K) pathway

PRINCIPLES OF USING THE IMMUNOLOGIC APPROACHES

Development of esophageal cancer (like all cancers) is predominantly due to failure of the body to eliminate normal cells that have become rogue. It is failure of the immune surveillance.[17,19] Recent insights have revealed the concept of brake and accelerator. Sometimes, the immune system is fooled into pressing the brake in the cancer identification and attack activity. Blocking the activity of $CD4^+$ and $CD8^+$ T cells results in blunting the local tumor-infiltrating immune responses.[18,20,21] This can happen due to secretion of immunosuppressive molecules such as transforming growth factor beta, interleukin (IL)-10, and vascular endothelial growth factor (VEGF); activation of negative signals to block PD-L1 and/or downregulation of the major histocompatibility complex Class I expression. Removing this blocking effect by appropriate therapeutic strategies can result in boosting the immune response akin to pressing the accelerator after the brake is removed. This can be achieved by the use of checkpoint inhibitors (that act by blocking inhibitory molecules or by activating stimulatory molecules) that unleash a robust anticancer immune responses (that had been chained so far) or harvesting the patients' T-cell and genetically modifying them (genetically engineered T-cells that recognize NY-ESO-1 or anti-MAGE-A3-DP4 protein on malignant cells) to enhance the immune system's anticancer response.[18,21]

HOW TO SELECT PATIENTS FOR IMMUNOTHERAPY

It is clear that a minority of all patients respond to current immunotherapy strategies and that responses can be documented after a significant delay (of weeks and even months), sometimes crossing the point of median survival. On the other hand, responders seem to do exceptionally well (including for years). Since immunotherapy comes at a high cost, enriching the population is a crucial unmet need.[20,21]

Till we have access to new and proven biomarkers, we are limited to the judicious use of PD-L1/PD-1 expression and tumor mutation burden. Some of the problems faced by us include PD-L1 expression heterogeneity, chronological variations (new patients vs. recurrent disease) and the effect of previous exposure to treatment. For patients on real time, PD-L1 expression increases with the cumulative dose of

radiation administered.[22] For patients given to neoadjuvant chemoradiotherapy, response leads to reduction in PD-L1 expression and may indicate the subgroup who no longer need further surgery.[23] However, this might also depend on the chemotherapeutic regimen used – platinum compounds and anthracyclines reduce PD-L1 as compared to taxanes and antimetabolites that increase their levels.[24,25]

Results of testing are also variable based on the nature of PD-L1 testing performed (pathological complete response vs. immunohistochemistry [IHC]) or the kind of reagents used (primers/antibodies). There is also lack of consensus on the cutoff value of PD-L1 positivity to be used for selecting patients (1% vs. 10% vs. 49% vs. 100%).

Interestingly, the pattern of PD-L1 in esophageal cancer is unique – staining in the malignant cells is less than that seen in the infiltrating non-malignant cells at the margin of invasion. It was seen in 29.9% (113/378) tumor cells versus 40.2% (152/378) in tumor-infiltrating cells in a report involving a total of 378 patients with advanced SS. In fact, prognosis was poorer among the patients whose tumor cells had high PD-L1 staining ($P = 0.009$).[26] On the other hand, if the patient was Epstein-Barr virus positive, PD-L1 expression correlated with better response and prognosis. Compounding our problems is the fact that expression can vary with age, degree of differentiation, stage, and timing of metastasis (if any). PD-L1 expression also had a direct correlation with MSI-high (MSI-H).[27]

Another biomarker of interest is the MSI phenotype. Initial interest was generated from its expression in a Phase I study of 15 patients correlating with response to pembrolizumab. Moreover, this also later on led to the US Food and Drug Administration (FDA) approval for pembrolizumab based on MSI-H phenotype expression.

Careful evaluation of these data has led to approval of the use of immunotherapeutic strategies and molecules for patients with advanced, unresectable, metastatic, or recurrent esophageal cancers having PD-L1 overexpression, MSI-H, or deficient mismatch repair features.

Other biomarkers that are promising include PD-L2 (high in about 50% of esophageal AC), NY-ESO-1, MAGE-A, LAGE-1, and TTK.[28]

Several publications from India have also revealed potential new biomarkers that might be useful in the future. One study from North India evaluated the role of O-6-methylguanine-DNA methyltransferase (a DNA repair gene). They studied 80 matched tumor and adjacent normal tissue for messenger RNA levels. It was detected to be downregulated and protein level absent in 52/80 tumor samples (65%) ($P > 0.001$).[29] Another study from Northeast India is also interesting because this population has unique dietary habits and distinct ethnic background. A total of 100 newly diagnosed esophageal cancers were compared to matched controls. Hypermethylation of p16 gene was seen in 81% of tumors versus absent among controls. The presence of p16 methylation and p53 variant/polymorphism (Pro/Pro or Arg/Pro) was higher among those who had a history of tobacco/betel nut consumption ($P = 0.037$).[30] It is known that gamma-delta T-cells use lymphocyte function-associated antigen-1, L-selectin, and CD44v6 to bind to SCC cells.

A study from western India analyzing tumor-infiltrating lymphocytes from esophageal carcinoma showed that there was accumulation of Vdelta1+ gamma-delta T-cells.[31]

IMMUNOTHERAPY OPTIONS AND STRATEGIES

a) Checkpoint inhibitors/immune modulators
b) Therapeutic peptide vaccines
c) Oncolytic viruses
d) Monoclonal antibodies and cytokines
e) Adoptive T-cell therapy.

PD-L1 inhibitors[17,21,32-44]

Nivolumab

The randomized, multicentric Phase III ATTRACTION 2 study in patients who failed at least two prior lines of CT has documented response in 493 heavily pretreated cases. Nivolumab (or placebo in a double-blind fashion) was given in dose of 3 mg/kg every 2 weeks till disease progression or unacceptable toxicity. The 12-month OS improved to 26.6% in the study arm versus 10.9% in the control arm. Similarly, ORR was 11.2% with nivolumab arm versus 0% with placebo arm. This improvement was found to be significant in both PD-L1-positive and PD-L1-negative tumors. Severe (Grade ≥3) adverse reactions were documented in 11.5% of cases on the study as compared to 5.5% in the placebo arm.

Japanese drug authorities gave approval to nivolumab based on this data.

The data from the follow-up ATTRACTION-3 study are now also available. Once more nivolumab demonstrated better OS – this time as compared to CT in previously treated (unresectable advanced or recurrent) patients with esophageal cancer.

Nivolumab became the first checkpoint inhibitor to provide a statistically significant improved OS – even in PD-L1-unselected cases.

Interest in combination immunotherapy strategies led to the CheckMate-032 study. Here, single agent nivolumab was compared to its combination with ipilimumab. This included 160 cases who had progressed earlier on standard CT. Among 96% (154/160) evaluable patients, overall response

rate (ORR) was 14% (nivolumab alone) as compared to 26% (for combination N1 plus I3 arm). When those with PD-L1+ tumors (more than 1% positive cells) were analyzed, ORR with nivolumab was 27% (4/15) versus 44% (4/9) in the patients on combination N1 plus I3 arm. This is collaborated by ONO-4538-12 study in advanced SS patients – with 17.2% achieved ORR and median OS of 12.1 months among 65 cases.

Logical extension was to evaluate the role in the adjuvant setting in the CheckMate-577 study. This involved use of nivolumab in 760 patients with resected Stage II/III esophageal cancer (both SS and AD). At present, this is the largest adjuvant study using checkpoint inhibitor in esophageal cancers and results are eagerly awaited.

Pembrolizumab

The multicenter, open-label, Phase Ib KEYNOTE-012 study with single-agent pembrolizumab for patients with PD-L1 overexpressed recurrent or metastatic cancers studied 39 cases. In 36 evaluable cases, the ORR was 22% (8/36) with 13% of the patients experiencing Grades 3–4 toxicity.

In the follow-up KEYNOTE-028 study used pembrolizumab in PD-L1^{+} advanced solid tumors including esophageal cancers, pembrolizumab was administered in the dose of 10 mg/kg every 2 weeks for PD-L1 overexpressing advanced cases. A total of 87% had ≥2 prior treatment for metastatic disease and 74% had SS histology. In 23 enrolled cases, the ORR was 30%, 12-month PFS was 21.7%, and medial duration of response was 15 months. The ORR was higher for AD [40%] versus SS [28%]. Four patients had Grade 3 treatment-related adverse events.

Pembrolizumab was combined with CT in the first-line KEYNOTE-059 study. It also included a maintenance phase. A total of 55% (143/259) had tumors overexpressing PD-L1 (IHC done using the 22C3 pharmDx Kit approved companion diagnostics). In these 143 cases, the ORR was 13.3% and 1.4% achieved an impressive complete response. Thus, pembrolizumab obtained approval by FDA for previously treated PD-L1 positive cases (with companion diagnostics using special scoring system).

A set back was the results from the Keynote-061 study that had randomized 592 patients between pembrolizumab and paclitaxel. There was no difference between the two arms for the whole group. However, there was some survival benefit over taxanes in a subgroup analysis and FDA gave approval for this drug in the third line setting. One limitation of this study was the fact that the current standard of care in this second line has already moved to a combination of paclitaxel and ramucirumab.

The ongoing Phase III KEYNOTE-062 study is evaluating pembrolizumab alone versus its combination with cisplatin plus 5-FU CT.

The Phase 2, open-label, single-arm KEYNOTE-180 study is for advanced, metastatic esophageal cancer that had progressed after two or more lines of CT. Of the 121 enrolled patients (data available up to March 21, 2017), 58 (47.9%) had tumors positive for PD-L1 by IHC (using a new cutoff score of 10 or higher). The ORR was 13.8% (8/58) and 5 patients (4.1%) discontinued treatment due to adverse events.

In addition, the Phase III KEYNOTE 585 study is with pembrolizumab in combination with CT in a neoadjuvant/adjuvant setting.

Other studies are evaluating pembrolizumab with radiation therapy (teletherapy and/or brachytherapy).

Thus, pembrolizumab is approved and beneficial in esophageal cancer patients with PD-L1 overexpression – responses being higher in AD (40.0%) versus SS (29.4%).

Avelumab

This is another immunotherapy drug under evaluation. The series of JAVELIN studies are currently evaluating the value of avelumab in several settings (locally advanced, metastatic, or recurrent; third line, second line, or maintenance phases).

Durvalumab

The NCT02639065 study is using durvalumab after completion of definitive therapy – for the 26 patients who have persistent residual esophageal cancer. The drug is also being evaluated for the second- and third-line metastatic cases, singly or in combination with tremelimumab.

Durvalumab is being evaluated in combination with ramucirumab (VEGFR-2 inhibitor) based on the hypothesis that they are capable of inducing a synergistic antitumor effect.

Most of the above drugs are also being evaluated in the neoadjuvant setting – either singly or as combination along with neoadjuvant CT/chemoradiation.

Therapeutic peptide vaccines

The vaccine complex (IMF-001; CHP-NY-ESO-1) has a recombinant NY-ESO-1 protein along with the cholesteryl hydrophobized pullulan. It is being studied for SS esophageal cancers. It does seem to induce significant immunogenicity.

Oncolytic viruses

OBP-301 is the telomerase-specific oncolytic virus which is administered directly into the tumor endoscopically. It is being evaluated with radiation therapy in elderly patients. Early results are promising, with ORR of 50% (3/6) and two even achieving a CR.

Monoclonal antibodies and cytokines

The antibody-drug conjugate (ADC) sacituzumab govitecan (IMMU-132) is the humanized anti-Trop-2 monoclonal antibody linked to the active metabolite of irinotecan (SN-38). It has already received approval for other cancers (breast cancer, lung cancer, and pancreatic cancer) and is currently also being evaluated for esophageal cancers.

Tisotumab vedotin (HuMax) is an ADC, the monoclonal antibody being linked to the cytotoxic drug monomethyl auristatin E. It targets tissue factor (protein involved in tumor signaling and angiogenesis) and is being studied in several solid tumors, including esophageal cancers.

Cytokines like IL 12 may also have limited but promising role in esophageal cancers.

Adoptive T-cell therapy

Early efforts with genetically engineering CD4 T-cells to target the MAGE-A3 protein (expressed in several solid tumors) failed to show benefit.

The chimeric antigen receptor T-cell therapy is gained the limelight after it was approved by the US FDA and more recently by NICE, UK. Its role in solid tumors and particularly esophageal cancer awaits evaluation.

Adverse effects

Immuno-strategies are not without unexpected and/or serious adverse effects. We are still learning how to anticipate, identify, and treat them.

Symptoms such as cough, breathlessness, or hemoptysis need to be reported by patients immediately for careful evaluation. Pneumonia, interstitial lung disease, and reactivation of pulmonary tuberculosis are potential problems that can progress rapidly with serious consequences. Autoimmune effects on skin, visceral organs (liver, kidneys, and heart), and endocrine glands (thyroid, etc.) are other potential issues needing appropriate intervention.[45]

One case of severe esophageal stenosis has been reported recently in a patient on nivolumab. Stenosis was relieved with tocilizumab (anti-IL6 receptor MoAb).[46]

Severe immunotherapy associated adverse effects could require temporarily or permanently discontinuation of the drug, need high doses of corticosteroids or both.

CONCLUSIONS

Immunotherapy strategies are rapidly gaining an emerging role in advanced esophageal cancer patients. At present, available and better biomarkers are required to select patients most likely to benefit. In the metastatic and recurrent settings, we are likely to get ORR of up to 15–25% in unselected patients (and up to 40% for PD-L1 overexpressing patients).

The ATTRACTION-3 provided landmark results – for the 1st time, a checkpoint inhibitor showed OS advantage in unselected heavily pretreated patients with esophageal cancer.[47]

Benefit of combination immuno-oncology drugs is being evaluated currently. The nivolumab/ipilimumab combination has already demonstrated an ORR of 21% when used in heavily treated cases.

The exact role of such molecules and combinations in various settings for esophageal cancer await the results of ongoing studies – in advanced/metastatic/adjuvant/neoadjuvant/perioperative studies.

To ensure optimal management, careful attention to understanding adverse effects is mandatory. Cooperation from patients in reporting new symptoms promptly is the only way by which new and potentially life-threatening adverse effects can be minimized. This is especially vital for India and other countries in the South Asian continent, where tuberculosis is still highly prevalent.

Global collaboration, free exchange of data, and online resources will ensure that the advances in management of esophageal cancers will be available worldwide.

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Conflicts of interest

There are no conflicts of interest.

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