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PROGNOSTIC SIGNIFICANCE OF PD-L1 IN HEAD AND NECK SQUAMOUS CELL CARCINOMA- AN AMBISPECTIVE STUDY

Oncology

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ABSTRACT

Introduction: Head and neck squamous cell carcinoma (HNSCC), derived from squamous epithelium of the upper aerodigestive tract, is the most common malignancy in the head and neck region with over 600,000 new cases diagnosed each year. While many of the HNSCCs may be detected in early stages, nearly 50% of the patients have lymph node metastasis at the time of diagnosis and 20-30% of the cases tend to have recurrence or distant metastasis within first 2 years of treatment of the primary Tumour. Even with multimodality approach with surgery, radiotherapy and chemotherapy, the outcomes are often dismal in Locally Advanced HNSCC. Hence , identification of novel biomarkers and potential molecular candidates for targeted therapy is necessary and one such promising candidate is the Immune Checkpoint Regulator Programmed Death Ligand-1(PD-L1). **Objectives:** The objective of this study is to identify PD-L1 expression in HNSCC and to identify the correlation between PD-L1 expression (as estimated by IHC) and clinicopathological parameters—including prognosis—in unresectable, metastatic and recurrent HNSCC cases presenting to a tertiary care centre in North Chennai

Material And Methods:

STUDY DESIGN- Ambispective study

STUDY SETTING- Government Stanley Hospital, Chennai, Tamil nadu

STUDY DURATION – January,2020 to June,2022

STUDY POPULATION – Patients with biopsy proven unresectable, metastatic or recurrent HNSCC who presented to the Department of Medical oncology, Government Stanley Hospital during the study period

All the cases with HPE proven unresectable, metastatic and recurrent HNSCC who have not received Radiotherapy or Chemotherapy prior to sample collection were included in the study. Patient's demographical and clinical characteristics were recorded. PD-L1 was estimated using IHC method. **Results:** 95 cases of locally advanced, unresectable or recurrent HNSCC were included in the study. Median age at diagnosis was 53 years. Male: Female=6:1. Localisation of the disease was as follows-: Oral cavity-48(50.5%), Oropharynx-15(15.8%), Larynx-16(16.8%), Hypopharynx-15(15.8%) and 1 case with lesions in all sites. 89 patients presented in locally advanced, inoperable stage and 6 patients underwent primary radical surgery followed by recurrence. Biopsy samples of all the patients were collected and PD-L1 was estimated by IHC and Combined Positive Score(CPS). PD-L1 positivity was noted in 38 cases(40%) of which strong intensity(CPS>_20) was noted in 11(11.6%) individuals and low staining intensity was noted in 27(28.4%) cases. No correlation was observed between PD-L1 positivity and well known causative factors of HNSCC like tobacco and alcohol. There was no correlation between PD-L1 and tumour stage, lymph nodal involvement, tumour grade, site of the lesion or Performance status of an individual. A statistically significant correlation($P<0.05$) was noted between PD-L1 status and gender of the individual. Among 95 cases, response of 47 patients to primary treatment could not be assessed due to ongoing treatment/defaulters/death. Among the cases assessed, 38 cases(80%) showed residual disease , 6 cases with recurrence and 4 cases progressed while on Definitive Radiotherapy. Median survival from diagnosis is 5.5 months(Range=1). No statistically significant correlation was seen between PD-L1 and response to therapy or Overall survival. **Conclusions:** Generally, it is assumed that PD-L1 enhances an aggressive tumor phenotype by allowing tumor cells to evade the host immune system by establishing an immunosuppressive microenvironment. Our study could not establish the role of PD-L1 as an independent prognostic cancer in Locally advanced or Recurrent HNSCC. The high prevalence of PD-L1 in HNSCC may be studied further to provide complementary therapies targeting the PD-1/PD-L1 pathway, and improve response to treatment.

KEYWORDS

INTRODUCTION:

Head and Neck Squamous Cell Carcinomas(HNSCC) refer to malignancies arising from the upper aerodigestive tract including lips, oral cavity, oropharynx, larynx, sinonasal cavities and nasopharynx[1].Owing to lifestyle changes, tobacco and alcohol consumption, increased Human Papilloma Virus (HPV) infections etc, there is an increase in the incidence of HNSCC not only in India, but also the World.

While many of the HNSCCs may be detected in early stages, nearly 50% of the patients have lymph node metastasis at the time of diagnosis and 20-30% of the cases tend to have recurrence or distant metastasis within first 2 years of treatment of the primary Tumour. Even with multimodality approach with surgery, radiotherapy and

chemotherapy, the outcomes are often dismal in Locally Advanced HNSCC[2].Hence , identification of novel biomarkers and potential molecular candidates for targeted therapy is necessary and one such promising candidate is the Immune Checkpoint Regulator Programmed Death Ligand-1(PD-L1)[3].

MATERIALAND METHODS:

Objectives:

The objective of this study was to identify PD-L1 expression in HNSCC and to identify the correlation between PD-L1 expression (as estimated by IHC) and clinicopathological parameters—including prognosis—in unresectable, metastatic and recurrent HNSCC cases presenting to a tertiary care centre in North Chennai

Conduct – The study was an Ambispective study, whose Protocol was approved by the institutional ethics committee. The study was conducted in accordance with the principles laid down by the declaration of Helsinki and the International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) guide- lines. The study was also in accordance with the Human Clinical Trial guidelines laid down by ICMR and Local Institutional committee.

Case selection- The data of the cases included in the study were collected from the prospective data base maintained in the Department of Medical Oncology at our tertiary care centre, after subjecting them to below mentioned inclusion criteria:

1. Age>18 years
2. Histopathologically proven Squamous cell carcinoma of Head and Neck
3. Locally advanced, unresectable/inoperable or recurrence cases
4. ECOG PS 0-2
5. Study period from January, 2020 to June, 2022

All patients selected for the study had to include all of the above mentioned criteria. From the prospective data base and patient's case files, clinical and demographic information including disease presentation, reason for offering CRT, course of treatment , compliance to therapy and response assessment were documented.

Hisptopathology blocks containing biopsy specimens of all the included cases were collected. Rabbit monoclonal PD-L1 (Cat PR303) was used with adequate control to assess PD-L1 by IHC method. PD-L1 protein expression in HNSCC was determined by using Combined Positive Score (CPS), which is the number of PD-L1 staining cells(tumour cells, lymphocytes, macrophages) divided by total number of viable tumour cells, multiplied by 100.

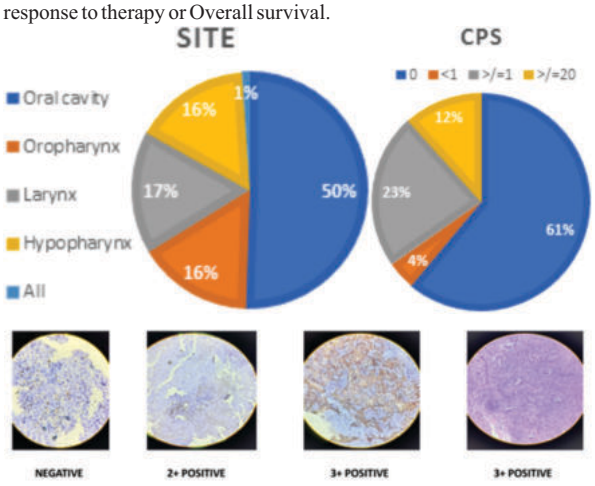
Statistical analysis was performed using Chi-square test to identify the correlation between PD-L1 expression (as estimated by IHC) and clinicopathological parameters—including prognosis—in unresectable, locally advanced HNSCC and Kaplan- Meier analysis was used to estimate survival .

RESULTS:

95 cases of locally advanced, unresectable or recurrent HNSCC were included in the study. Median age at diagnosis was 53 years. Male: Female=6:1. Localisation of the disease was as follows-: Oral cavity-48(50.5%), Oropharynx-15(15.8%), Larynx-16(16.8%), Hypopharynx-15(15.8%) and 1 case with lesions in all sites. 89 patients presented in locally advanced, inoperable stage and were treated with Definitive chemoradiation with 66Gy in 33 fractions along with administration of weekly Cisplatin at a dose of 30 mg/m2. 6 patients underwent primary radical surgery followed by recurrence.

Biopsy samples of all the patients were collected and PD-L1 was estimated by IHC and Combined Positive Score(CPS). PD-L1 positivity was noted in 38 cases(40%) of which strong intensity(CPS>_20) was noted in 11(11.6%) individuals and low staining intensity was noted in 27(28.4%) cases. No correlation was observed between PD-L1 positivity and well known causative factors of HNSCC like tobacco and alcohol. There was no correlation between PD-L1 and tumour stage, lymph nodal involvement, tumour grade, site of the lesion or Performance status of an individual. A statistically significant correlation($P<0.05$) was noted between PD-L1 status and gender of the individual.

Among 95 cases, response of 47 patients to primary treatment could not be assessed due to ongoing treatment/defaulters/death. Among the cases assessed, 38 cases(80%) showed residual disease , 6 cases with recurrence and 4 cases progressed while on Definitive Radiotherapy. Median survival from diagnosis is 5.5 months(Range=1). No statistically significant correlation was seen between PD-L1 and response to therapy or Overall survival.



PD-L1 estimation by IHC

CHARACTERISTIC	TOTAL	PD-L1 POSITIVE	PD-L1 NEGATIVE	P value
All HNSCC cases	**95**	**38(40%)**	**57(60)**	
Age	**95**			
<50 yrs	38(40%)	16(42.1%)	22(57.9%)	
51-60 yrs	33(34.7%)	17(51.5%)	16(48.5%)	0.62
>60 yrs	24(25.3%)	5(20.8%)	19(79.2%)	
Gender				
Male	82(86.3%)	28(34.1%)	54(65.9%)	0.005
Female	13(13.7%)	10(76.9%)	3(23.1%)	
Smoking status				
Non smoker	17(17.9%)	7(41.2%)	10(58.8%)	
Smoker	61(64.2%)	21(34.4%)	40(65.6%)	0.334
Tobacco chewer	14(14.7%)	8(57.1%)	6(42.9%)	
Betel nut chewer	3(3.2%)	2(66.7%)	1(33.3%)	
Alcohol consumption				
No alcohol	25(26.3%)	11(44.0%)	14(56.0%)	0.634
Alcohol	70(73.7%)	27(38.6%)	43(61.4%)	
Performance status(ECOG)				
0	1(1.1%)	0	1(100%)	
1	33(34.7%)	13(39.4%)	20(60.6%)	0.765
2	57(60%)	24(42.1%)	33(57.9%)	
3	4(4.2%)	1(25%)	3(75%)	
Site				
Oral cavity	48(50.5%)	24(50%)	24(50%)	
Oropharynx	15(15.8%)	4(26.7%)	11(73.3%)	0.132
Larynx	16(16.8%)	3(18.8)	13(81.2)	
Hypopharynx	15(15.8%)	7(46.7%)	8(53.3%)	
Combined	1(1.1%)	0	1(100%)	
T stage				
1	3(3.2%)	2(66.7%)	1(33.3%)	
2	15(16%)	7(46.7%)	8(53.3%)	0.844
3	27(28.7%)	11(40.7%)	16(59.3%)	
4a	44(46.8%)	16(36.4%)	18(63.6%)	
4b	5(5.3%)	2(40%)	3(60%)	
N stage				
0	12(13%)	4(33.3%)	8(66.6%)	
1	16(17.4%)	8(50%)	8(50%)	0.822
2	54(58.7%)	21(38.9%)	33(61.1%)	
3	10(10.9)	4(40%)	6(60%)	

Grade				
Well differentiated	29(30.5%)	12(41.4%)	17(58.6%)	
Moderately differentiated	64(67.4%)	26(40.6%)	38(59.4%)	0.505
Poorly differentiated	2(2.1%)	0	2(100%)	
Response to treatment				
Not assessed	47(49.5%)	16(34%)	31(66%)	
Partial response/Residual disease	38(40.0%)	15(39.5%)	23(60.5%)	0.211
Complete response	6(6.3%)	4(66.7%)	2(33.3%)	
Progressive disease	4(4.2%)	3(75%)	1(25%)	

DISCUSSION-

Compared with the traditional treatments, the up and coming Anti -PD-1/PD-L1 agents present better efficacy and lower toxicity for patients with advanced HNSCC [5-8]. The Overall Response Rates of Nivolumab and Pembrolizumab are only 15% for HNSCC, indicating that much more effort should be made to investigate the pattern and mechanisms of PD-1/PD-L1 expression in HNSCC[9] . Several studies were done earlier to elucidate PD-L1 prevalence in HNSCC.

STUDY	Sample Size	Cut off for PD-L1 positivity	% positivity	Site of lesion(Squamous cell carcinoma)
Lyford-Pike et al.[10]	27	5% of tumour cells	59%	Oropharynx
Kim et al.[11]	133	20% membrane staining of tumour cells	68%	Oropharynx
Hong et al.[12]	99	Unequivocal membrane staining of tumour cells	69.7%	Tonsil
Mattox et al.[13]	53	1%membrane staining of tumor and/or immune cells	79%	Tongue
Balermpas et al.[14]	161	5%of tumor and/or stromal cells	39.1%	All HNSCC
Ou et al.[15]	38	1% on both tumor and immune cells 5% on both tumor and immune cells	71% 50%	All HNSCC

The findings in our study are similar to above mentioned studies with a prevalence of 40%. Our study showed that response to Definitive chemoradiation is sub-optimal. One caveat in our study is the usage of Cisplatin at a dose of 30 mg/m2, which may have contributed to the sub-optimal response. Nevertheless, we would like to emphasise that based on age and other comorbidities, many patients may not tolerate Cisplatin at a dose of 40 mg/m2 and hence exploration of other treatment options is essential.

CONCLUSION-

HNSCCs when present in locally advanced, unresectable stage have not shown to respond well with local modality of treatment and novel options need further exploration. High prevalence of PD-L1 in HNSCC makes it an ideal therapeutic option.

Generally, it is assumed that PD-L1 enhances an aggressive tumor phenotype by allowing tumor cells to evade the host immune system by establishing an immunosuppressive microenvironment[4]. Our study could not establish the role of PD-L1 as an independent prognostic cancer in Locally advanced or Recurrent HNSCC. The high prevalence of PD-L1 in HNSCC may be studied further to provide complementary therapies targeting the PD-1/PD-L1 pathway, and improve response to treatment.

CONFLICT OF INTEREST-

The author declares no conflict of interest

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No financial aid was taken for this study

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