

IDO1 and CXCL11 mRNA gene expressions, adjusted for TP53 genomic aberrations and PD1/PDL1 mRNA gene expressions, are prognostic in patients with stage III-IVB HPV-negative HNSCC

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Abstract

Objective: IDO1 expression has been identified as both a favorable and unfavorable prognostic marker in different cancers and CXCL11 is an inflammatory marker involved in both T cell recruitment and tumor cell migration. We sought to determine the prognostic role of IDO1 and CXCL11 in patients with stage III-IVB HPV-negative HNSCC while controlling for TP53 genomic aberrations and PD1 and PDL1 immune mRNA expressions.

Methods: Using 319 patients in The Cancer Genome Atlas with pathologic stage III-IVB HPV-negative HNSCC, we performed Cox regression analyses of combined high (upper quartile) IDO1 and CXCL11 mRNA expressions according to locoregional or distant failure (LRDF) and overall survival (OS).

Results: For LRDF, a combined score of IDO1 and CXCL11 (HR: 0.40, P=.03) was associated with a lower risk, while the presence of ENE and advancing age at diagnosis were associated with increased risk. For OM, a combined score of IDO1 and CXCL11 (HR: 0.36, P =.005) and the delivery of adjuvant radiotherapy were associated with lower risk, while a combined mRNA expression score of PD1 and PDL1, nonsense TP53 mutations, advancing age at diagnosis, presence of ENE, and oral cavity subsite were associated with increased risk.

Conclusion: Controlling for TP53 genomic features, PD1/PDL1 mRNA expression, and clinicopathologic factors, increased IDO1 and CXCL11 mRNA expressions are associated with lower risks of LRDF and OM. Further validation is warranted.

Introduction

- TP53 is the most common genomic aberration in HPV-negative HNSCC, and destructive mutations portend a worse prognosis¹
- IDO1 is a rate-limiting enzyme in tryptophan metabolism that is thought to play an important role in the decision between an immunogenic and tolerogenic response to chemo- and radiotherapy induced tumor cell apoptosis^{2,3}
- CXCL11 is an inflammatory marker that interacts with CXCL9,-10 and CXCR3 to promote immune activation, tumor proliferation, angiogenesis, and metastasis^{4,5}
- IDO1 and CXCL11 may have prognostic utility in HPV-negative HNSCC due to their role in inflammation, immune response, and tumor proliferation

Methods

- We performed Cox regression analyses of IDO1 and CXCL11 mRNA expression according to LRDF or OM
- The study included 319 patients in The Cancer Genome Atlas with stage III-IVB HPV-negative HNSCC of the oral cavity, oropharynx, larynx, and hypopharynx treated with surgery +/- adjuvant radiotherapy and chemotherapy
- The analysis was adjusted for TP53 genomic aberrations and PD-1/PD-L1 mRNA expression
- We tested for significant demographic, clinicopathologic and treatment-related confounding variables including age, race, sex, smoking and alcohol use, perineural invasion, lymphovascular space invasion, close/positive margins, extranodal extension (ENE), number of pathologically involved lymph nodes, anatomic subsite, pathologic stage, and adjuvant therapy delivered
- All tests were two-tailed, P <.05 indicated statistical significance

Results

Locoregional or Distant Failure (87 events, 5-year cumulative incidence = 38.2%)

Variable	HR	P value	95% CI
Combined IDO1 and CXCL11	0.40	0.03	0.18-0.90
Presence of ENE	3.20	<0.001	1.70-6.02

Overall Mortality (153 deaths, median overall survival = 3.29 years)

Combined IDO1 and CXCL11	0.36	0.005	0.18-0.74
Combined PD-1/PD-L1 expression	2.72	0.02	1.14-6.43
Nonsense TP53 mutation	2.03	0.01	1.15-3.52
Presence of ENE	2.13	0.004	1.27-3.58
Oral cavity subsite	1.69	0.03	1.04-2.75

Conclusion

- Increased IDO1 and CXCL11 mRNA expression is associated with lower risk of locoregional or distant failure and overall mortality in HNSCC when controlling for destructive TP53 mutations and PD1/PDL1 expression
- Integrated immune marker expression of IDO1 and CXCL11 may help inform future clinical studies
- Further validation of the prognostic role of CXCL11 and IDO1 in HNSCC is warranted
- These findings contribute to our understanding of the complex tumor microenvironment and immune response in HNSCC

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