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MANAGEMENT OF HPV RELATED OROPHARYNGEAL CANCER-A REVIEW ABOUT TREATMENT

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ABSTRACT

Human papillomavirus (HPV)-associated oropharyngeal cancer (OPC) has emerged as a growing public health concern worldwide. This review focuses on the current understanding and management strategies for HPV-related OPC. The rising incidence of this malignancy highlights the need for comprehensive insight into its epidemiology, transmission, etiology, genomic organization, pathogenesis, diagnostic methods, and available treatment options. The article examines conventional and emerging therapeutic approaches, including chemoradiotherapy (CRT), immunotherapy, surgical innovations, and targeted medical treatments. Notably, recent progress in immunotherapeutic interventions has shown encouraging potential in improving treatment outcomes. This review also addresses the effectiveness and side effects of these therapies, with particular attention to their impact on patients' quality of life and long-term survivorship. Additionally, it underscores the critical role of HPV vaccination in primary prevention and provides an overview of ongoing clinical trials. The insights presented aim to support clinicians, healthcare professionals, researchers, and policymakers in enhancing the management and prevention of HPV-related OPC.

INTRODUCTION

Human papilloma virus (HPV) possesses a circular shape and double DNA strands, with approximately 8000 pairs of bases, from Papillomaviridae family and transmitted via sexual interactions. It affects both men and women. On the base of ability to cause cancer via persistent infection, it has been categorized into high and low-risk groups. High risk are strongly associated with oropharyngeal and cervical malignancies. HPV virus infiltrates the deepest basal layer of the epithelium taking advantage of any minor imperfection or disruption in the mucous barrier; as these ground cells transform into squamous epithelium, HPV DNA proliferates aggressively and creates a high concentration of copies (Minhas et al., 2022; Okami, 2016).

HSCNN poses a striking threat to the health sector around the world and also secures the sixth place as most frequent cancer globally. 90 % of HNSCC comprises squamous cell carcinomas. Even though OPSCC accounts for only 0.9% of all cases still its frequency is ascending worldwide(F De Felice et al., 2019; Elrefaey, Massaro, Chiocca, Chiesa, & Ansarin, 2014).Infection by HPV reported to be 9.7% common among healthy oral mucosa, based on several studies, primarily connected in Karachi, Pakistan(Minhas et al., 2022).

Over 100 various strains of HPV have been revealed, with 15 types believed to carry an elevated chance of causing cancer. Among these 15 strains, HPV-16 causes the 90% cases. In comparison to patients without HPV cancer, those who were positive typically exhibit younger ages(Kofler, Laban, Busch, Lörincz, & Knecht, 2014). Reduced tobacco usage has been associated to reduction in the occurrence of HNSCC, whereas growing HPV-OPC rates are connected to the quantity of sexual partners(Urban, Corry, & Rischin, 2014). The use of marijuana could be one of the element that contribute. Conversely, severe alcohol consumption, improper dental care and smoking tobacco are closely linked to non HPV cancer patients while sexual behavior or marijuana are not (Peres, 2010).

Improved clinical outcomes and enhanced survival chances for patients tend to be correlated with oropharyngeal carcinoma result from HPV. It seems that the molecular basis of neck and head cancer caused by HPV is unlike that of head and neck cancer not caused by HPV(Haigentz et al., 2009). As stated in recent research, the distinctive molecular feature unique to HPV-OPC along with the patient's immune responses that this particular tumor generates might contributes to improved life expectancy. Unlike negative HPVOPC, the positive patients might be more susceptible to therapy-induced DNA damaging effects because of its increased capability to maintain important molecular regulators of biological aging and apoptosis(Fung, Faraji, Kang, & Fakhry, 2017).

The multidisciplinary unit employed a wide array of methods to confront the disease at its beginning and remotely, whether through medical or non-medical means. A predominating staging method named as TNM (tumor-node-metastasis) provided by the American Joint Committee (AJCC) is utilized for OPC. Considering precise staging (I to IV) relies on factors particular to patient such as location of tumor, lymph node and extension status. It plays pivot role when it comes to management of patients with HPV. According to latest recommendations, a combination therapy including primary surgical treatment and following surgery chemo radiotherapy or ultimate combined chemo radiotherapy (CRT) which is cisplatin-based, is the standard of treatment for patient with dense and regionally spreading OPSCC or detrimental pathological features. However, considerable toxicities are known to occur with combined therapy both, early and late. For any comeback or spread of the malady, salvage activity or renewed irradiation should be reconsidered (Bigelow, Seiwert, & Fakhry, 2020; Deschuymer, Mehanna, & Nuyts, 2018; Ward et al., 2015).

This article give us a view on the complex network of treatment options available for oropharyngeal cancer linked to HPV. We dive into the range of techniques accessible to oncologists to combat this specific cancer, from classic traditional method like surgery and radiation therapy to ground breaking advancements in chemo and radiotherapy. We also discuss the crucial role played

by multidisciplinary care teams to create personalized programs that take in to the consideration the distinct attributes of patient's illness for maximum therapeutic results.

Our main purpose is to provide the patients, attendants and health professionals a better grasp of complexities a better grasp of obstacles in handling of this illness. For those who are succumb to oropharyngeal cancer due to HPV, for improved patient treatment and standard of life by closely examining current techniques and emerging researches, is our main aim.

TRANSMISSION

HPV is assumed to be transmitted by mucosal skin contact, sexual contact and specifically oro-genital interaction at oropharyngeal sites(Kofler et al., 2014). Possibly, another way HPV can transfer vertically from mother to infant is during birthing process. HPV aims at cells that exhibit the capacity to differentiate into keranocyte, located in skin and mucosal germ cell layers(Morshed, Polz-Gruszka, Szymański, & Polz-Dacewicz, 2014).The characteristic warts formation by HPV at various sites including oro-genital mucosa, skin, throat and urethra allows direct contact transmission(Bharti, Chotaliya, & Marfatia, 2013; Morshed et al., 2014)

ETIOLOGY

Traditional danger indicator like drinking and smoking tobacco and HPV positive malignancies have no correlation in most cases(Zur Hausen, 2002). Nowadays, growing evidence indicates positive HNSCC due to HPV is transmitted sexually (Marklund & Hammarstedt, 2011). People vulnerable to HPV infection, growing evidence indicates association between sociodemographic characteristics and continuous oral sexual practices(Wierzbicka, Klussmann, San Giorgi, Wuerdemann, & Dikkers, 2021).There is a heightened likelihood for women and their spouses to develop tonsils tumor, who have cervical cancer(Marklund & Hammarstedt, 2011). The likelihood of HPV positive HNSCC to occur has been linked to sexual conduct. This contains having multiple sex partners for vaginal and oral sex, engaging in sexual activities at an early age along with history of genital warts (Gillison et al., 2008; Kreimer et al., 2004; Schwartz et al., 1998). Highly risky infection of HPV on mucosa of oral cavity and positive serology boosts the chance to develop HNSCC. It is believed that development of HPV positive HNSCC is followed by HPV infection (D'Souza et al., 2007; Mork et al., 2001; Smith et al., 2004). HPV- positive mother's newborns and infants are rarely seen acquiring HPV infection in oral cavity. The children of affected mother remain uninfected until they become sexually active(Marklund & Hammarstedt, 2011). Personal habits that have been looked into are marijuana consumption and poor oral health practices. Probability of getting HPV-16 HNSCC escalated with marijuana abuse, although correlation with inadequate oral health was not found according to latest reports(Gillison et al., 2008). Evidences suggests despite taking medication against retro viruses individuals with HIV are more inclined to get tumor formation via HPV(D'Souza et al., 2007; Marklund & Hammarstedt, 2011). Fanconi anemia patients are also highly vulnerable to HPV related anomalies (Adamopoulou et al., 2008; Marklund & Hammarstedt, 2011).

VIRAL GEMONE ORGANIZATION

Human papillomavirus has the capacity to infect and change epithelial cells and explicitly focuses on the basal cells of epithelial mucosa (Markopoulos, 2012). The extent to which it infects can be partitioned into two kinds: low-risk and high-risk types. The type with generally low- risk are related with growth of benign lesions like warts, while high-risk type disease might advances to threatening malignant lesions (Groves & Coleman, 2015). HPVs are DNA, non- enveloped microorganism that additionally contain icosahedral capsids and replicate their genome in infected host cell nuclei (Longworth & Laimins, 2004).

The viral genome is coordinated into three segments: an early region (E), a late region (L) and a genomic regulatory region. The early region addresses 50% of genome and consist of E1, E2, E4-E7, while the late region addresses 40% of the genome and comprises of L1 and L2, while the

genomic regulatory region covers 10% of the genome. These L1 and L2 are major and minor capsid proteins respectively (Morshed et al., 2014). The viral genome contains onco proteins encoded by these regions that are liable for HPV- gene regulation and cell transformation. E1 protein is vital and fundamental replication component. It acts as the origin recognition protein as well as a repressive agent in transcription and inhibits DNA replication (Wilson, West, Woytek, & Rangasamy, 2002). Protein E2 is a transcriptional factor, yet in addition, it is engaged with the DNA replication process. It performs essential part in coding proteins, which directs viral DNA transcription. E2 is likewise answerable for cell change, starting and limiting apoptosis, transcriptional regulation, and transformation capability of HPV. E2 inactivation influences the advancement of cancer sores by enhancing the impression of E6 and E7, and dynamic E2 represses the transcription of E6 and E7, causing an expansion in p53 expression and apoptosis of the spoiled cells. The protein is necessary for keeping up with the replication of the infection and the blend of the qualities through the course of the differentiation cycle of the epithelium (Miller, Puricelli, & Stack, 2012; Morshed et al., 2014).

E4 protein is a cytoplasmic protein that upsetting the primary structure of keratin. Because of protein E4 activity, the thickening of the spinous takes place and its presence in abscesses suggests its part in the arranging of horny layer of the epidermis, and the koilocytosis of the epidermis happens. The observations gave ideas for the significance of the E4 biomarker in the determination and sickness organizing. E4 proteins are noticeable during the high level phases of the infection, around the hour of genome enhancement commencement. Additionally, it has been expressed that E4's capability to upset the cell keratin gateway and the aggregation of cornified envelope might assist the arrival of the infection or potentially its transmission. E5 is an 83 amino acid hydrophobic protein that subsequently confines to film-bound compartments. HPV E5 enacts epidermal growth factor receptor (EGFR) and intercedes for improvement of EGFR signaling, prompting expanded articulation of vascular endothelial growth factor (VEGF). Both E4 and E5 proteins are linked early, with the capability to adjust the late period of the viral life cycle (Kim et al., 2006; Miller et al., 2012; Morshed et al., 2014). E6 and E7 proteins accept a central role in HPV-subordinate malignant change. These proteins cause an impairment in the control of cell cycle regulation and cell development. The viral oncoproteins E6 and E7 tie p53 and pRb (protein retinoblastoma) reciprocally. The resultant impact is that E6 confining cause p53 debasement, while E7 limiting to pRb and p21 prompts the inception of transcriptional factors. These transcriptional factors make malignant cells headway in the cell cycle, which is unopposed on account of the lack of p53 (Swiecicki, Malloy, & Worden, 2016).

PATHOGENESIS

The HPV life cycle is completely connected to the differentiation phase of the infected epithelial cells (Morshed et al., 2014). As the skin have several layers: basal cell layers on top of the basement membrane, spinous layers, and cornified cell layers, through a wound or micro- abrasion, HPV first attaches itself to the basement membrane of the body. The virus injects its DNA into the nucleus of the cell, following its access to basal cells. As the basal cell matures, infected cells make their way to the very top and start proliferation and replication. There are only 13 types of HPV that are associated with cancer. It causes cancer by infecting stem cells within the basal cell layer, hijacking the machinery of host cells as it matures, and producing more and more DNA as it replicates. Malignant lesions form as the cancerous cell replicates even faster than the immune system of the host can reach it (Burd, 2003).

DIAGNOSIS

When it comes to the correct diagnosis of OPSCC it demands HPV testing for further prognosticating (Taberna et al., 2017), still the debate over ideal diagnostic technique is still up (Chai, Lambie, Verma, & Punyadeera, 2015). A range of diagnostic methods available ranging from HPV- DNA detection via polymerase chain reaction (PCR), ISH (in situ hybridization) in biopsy

samples. E6/E7 mRNA assessment of HPV by ISH and RT-PCR (reverse transcriptase), each technique possess specificity and sensitivity profile of their own. E6/E7 mRNA inspection is accepted as golden standard for potentially reveal HPVs undergoing transcription and verifying its causation (Taberna et al., 2017).

Tumor masses lateral to neck are the frequently observed feature of OPSCC by HPV and significant portion of patients arrive when they have localized metastases pointing towards the progressed stage of disease. Thus, to achieve fruitful and less invasive therapy demands a technique which can potentially recognize concealed lesion. Individual at high risk can be screened for the presence of regional masses through promising positive antibody (serology) testing and imaging (Timbang et al., 2019).

SEROLOGICAL DIAGNOSIS

Recent researches have shown high association of E1, E6 and E7 antibodies-HPV16 in both individuals with OPSCC and healthy ones when compared (Anderson et al., 2011). HPV16- OPSCC patients with positive serology of E6 and E7 demonstrated a positive overall survival in contrast to negative serology (Liang et al., 2012). In an initial study, it revealed 14 folds heightened risk to get OPSCC who exhibited antibodies against L1 protein in HPV16 capsid. This concluded by data merging among tumor records and Nordic serum bank (Mork et al., 2001; Timbang et al., 2019).

Utilizing IgG presence in serum against the virus act as valuable indicator to figure out whether infection is ongoing or it was in the past. An elevated danger to have infection in positive HPV cases was seen having virus-specific IgG in saliva and sera in study conducted by Cameron et al (Chai et al., 2015). Since serology bio indicators lack location specificity, they might show up form infections at locations other than mouth cavity, which compromises specificity of testing method (Mork et al., 2001).

DNA DETECTION BY PCR

PCR is detection criteria is highly sensitive and economical for various kinds of HPV, intact L1 open reading frame (ORF) is the focus of primer. For the examination of broad spectrum of HPV primer pairs like GP5/GP6 and MY06/MY11 are widely employed (de Roda Husman, Walboomers, van den Brule, Meijer, & Snijders, 1995). As a result of incorporation of viral DNA cell being infected can preserve carcinogenic E6/E7 sequences. This makes PCR technique aiming on these oncogenic sequences quite sensitive in HPV identification (Noffsinger, Suzuk, Hui, Gal, & Fenoglio-Preiser, 1995). In E6 and E7 sections there exist quite a difference among HPV variants (Bernard, Calleja-Macias, & Dunn, 2006). Not only evidence of HPV but also low and high risk variants can be confirmed via designable primers for E6/E7. HPV originated from tumor or normal stroma can't be differentiated by conventional PCR for having limited specificity. PCR lacks capacity to discriminate between episomal and embedded DNA results in poor detection of clinically serious infection. There is lack of established PCR to apply clinically for now and specificity and sensitivity for this vary among labs. Data updates shows PCR paired with quality control reagents and a uniform procedure display remarkable consistency among labs (Kornegay et al., 2003).

IMMUNO HISTO CHEMISTRY (ISH)

ISH is an additional approach towards HPV detection, inclusions inside epithelial cells nuclei can be witnessed during ISH microscopy confirming virus presence. Reliable identification and topographical association with lesions makes ISH specific over PCR (Venuti & Paolini, 2012). As identified by ISH, a notable association was witnessed among p16 and the occurrence of HPV DNA (Singhi & Westra, 2010). As a proxy marker for identifying HPV in histological samples of HNSCCs, the IHC evaluation of p16INK4A in tumor tissues has been reported to working (Mendelsohn et al., 2010). Suppressor gene p16 enhance itself in tumor cells as compensatory mechanism, this happens when E7 binds to Rb of HR HPV following host cell non-proliferation

(Zhang, Postigo, & Dean, 1999). Patient were at considerably raised risk of every cause of death having absence of antibodies for HPV and p16 presence (Liang et al., 2012). Tumor p16 positivity is linked to higher prognosis, risk prediction in patients by IHC p16 is proved to be effective. But supported by above data, the hypothesis to utilize p16 over expression to detect HPV reliably is not sufficient. This technique has been declared as preferred one test by many healthcare professionals because it has been widely investigated, pocket friendly and has clear staining interpretation guidelines (Lewis, 2012). Other techniques also required for proper diagnosis, along with IHC in combination with RNA and DNA detection (Chai et al., 2015).

DETECTION OF RNA

A superior strategy compared to DNA is PCR approaches toward mRNA in producing clinically crucial HPV infection proof (Deng et al., 2013). The significance of cancerous transcripts in initiation and progression of tumor is highlighted by manifestation of mRNA originating from episomal or internalized DNA. The investigation revealed 48 out of 96 (50%) of positive HPV OPSCC samples had E6/E7 transcripts (Holzinger et al., 2012). Transcripts were found in 15 out of 54 (27.5%) of positive patients in samples. This demonstrated a notable correlation to a raised HPV-16 DNA content (Deng et al., 2013). This data proves substantial association among E6/E7 mRNA activity rate and abundant viral count, about 75% of individuals with OPSCC on tonsillar region via HPV have considerably grown E6/E7 mRNA levels as opposed to other oropharyngeal locations (Deng et al., 2013). A study involving OPSCC patients displayed 99.3% p16 tumor positivity, exhibiting greater sensitivity in ISH in contrast to DNA ISH (Chai et al., 2015). 97% of sensitivity and 93% specificity exhibited when OPSCC FFPE (formalin fixed paraffin embedded) samples due to HR HPV were evaluated utilizing RNA ISH (Schache et al., 2013). The findings exposed active and clinically significant HPV infection is in accordance with HPV transcripts identification, indicating potential inclusion in current protocols. Combined diagnostic strategies as in tumor HPV-DNA and RNA ISH paired with DNA PCR or p16 is productive. In case of positivity p16 leads the diagnostic path followed by PCR or ISH (Schache et al., 2013; Singhi & Westra, 2010).

ORAL DETECTION

Biological indicators found in oral fluid is being utilized with a particular focus, as in recent times HNSCC by HPV has become surge of interest (Chai et al., 2015). Various substances, including antibodies, steroids, hormones, cytokines, growth factors, chemokines and drugs, have been found in oral fluid, which can indicate both local and systemic health conditions (Lima, Diniz, Moimaz, Sumida, & Okamoto, 2010; Pfaffe, Cooper-White, Beyerlein, Kostner, & Punyadeera, 2011) . In oral secretions biological indicators are close to tumor for early HPV OPSCC evaluation and tracking of progressing illness. Non-imposing and profitable nature has made this method gain attention (Chai et al., 2015). A significant association was observed among variants of HR HPV in tumor and those found in mouth rinse, by inspecting oral cellular exfoliation from the tissues of HNSCC patients (Smith et al., 2004). According to recent investigation, detection of HPV in both tumor tissue and oral washings exhibited identical outcomes in terms of identification (Koslabova et al., 2013). To date, research conducted has yielded positive outcomes in using oral secretions as a dependable sample for identifying HR- HPV and other prognostic indicators. However, the clinical performance of this and other oral secretion based detection strategies lacks support by experimental data. Given the diverse origins of the cell being analyzed in oral fluid, additional advancements are essential in oral fluid based testing to detect HPV infection (Venuti & Paolini, 2012).

Saliva screening technique analyzes the existence of viral DNA and effective in specifically targeting HR-HPV16 and other high risk strains. Although this method can indicate a persistent infection, but it isn't reliable for detecting HPV-OPC as plenty of patients get rid of virus without developing malignancy. Consequently, it is not a recommended for screening purpose (Timbang et al., 2019).

TREATMENT

While the deep studies of reliable literature we reviewed the treatment strategies of HPV-related OSCC. These techniques include radiation therapy, chemotherapy and trans-oral surgery. This article also carries information about advanced strategies for HPVOSCC management. With time, some advances have been made, including potential changes in standard treatment protocols. The patients with younger age, longer life span and the quality of life (QoL) became vital issues supporting the examination of feasible de-escalation procedures that possibly could diminish morbidity associated with treatment-related toxicity levels without compromising persistence results (F. De Felice et al., 2019).

RADIATION THERAPY

Radiation works by using standard radiation dosage 70 Gy which damages the DNA of the tumor cells and making them unable to repair themselves or grow new cells. For OPSCC, radiation therapy (RT) to be effective in treating cancer, wide treatment fields and substantial dosages are needed. Radiation plus chemotherapy, also known as proton therapy, is a combination treatment protocol that is by far more demanding than surgery, with long-term effects such as significant weight loss, damage to salivary glands, loss of taste, and overall fatigue. With time, radiation therapy has developed into intensely modulated radiation therapy, or IMRT. This new radiotherapy technique works to try to reduce damage to health areas in the body, increase the accuracy and reduce the dose to bystander structures (A. Hay & I. J. Nixon, 2018). Intensely modulated means that the radiation comes in from different angles to focus the radiation in certain areas and spare other areas. Traditionally radiation would just come in from one side and out from the other side. Major possible benefits of this technique for conveying radiation include avoidance of high-portion exposure to the salivary glands (Nutting et al., 2011). But in the case of proton therapy, proton is kind of added to the multi-directional approach. HPV-positive OPC is sensitive to radiotherapy thus; the treatment associated with toxicity is a result of radiotherapy, which is caused by the radiation dose received by typical tissues (Dirix, Abbeel, Vanstraelen, Hermans, & Nuyts, 2009).

CHEMO-RADIO THERAPY

To proclaim a curative purpose, concurrent chemotherapy is advised (Network, 2016). Patients, who have a positive HPV-OPC prognosis for an extended period, display a stronger tendency to evade or reduce the harm associated with treatment. In light of this, researchers have strived to decrease toxicity by minimizing the dosage of radiation therapy or modifying and even eliminating the concurrent therapy (Deschuymer et al., 2018). Chemotherapy along with radiotherapy (RT) has been utilized to treat new or high-risk oropharyngeal malignant growths (OPC). Extra-capsular expansion (ECE) of positive lymph nodes and surgical margins are known to be high-risk factors that usually warrant adjuvant chemo-radiotherapy (CRT) (Shaw et al., 2010). Chemotherapy typically includes cisplatin (used as chemotherapy medication) that has been demonstrated to be powerful in OPC by acting as a radio-sensitizing agent. For this reason, it would make sense to treat OPSCC caused by HPV with concurrent chemotherapy and a lower radiation dosage. The addition of chemotherapy to adjuvant radiation has further developed survival in patients, however at the cost of increased acute toxicity (Hanasoge et al., 2016; W. Su et al., 2016). It is possible that cisplatin, which is utilized as a radio-sensitizing agent, may not be fundamental in select HPV+ growths, since they are inherently receptive to radiation. Concurrent cisplatin is much of the time given at lower doses with radiation as a radio-sensitizing agent, and as an only agent isn't optimized to treat metastatic illness. Chemotherapy along with radiation therapy regimens leads to enhanced acute treatment-related toxicity with late toxicity (Machtay et al., 2008). An important factor in the development of late toxicity is the dose that is administered to the surrounding tissues (De Felice et al., 2018). It may be possible to reduce toxicity via de-intensification RT techniques without compromising survival rates. Strategies for deescalating radiation dosage are presently being

researched (Nuyts et al., 2013).

USE OF CETUXIMAB TO REDUCE TOXICITY

For reduction of toxicity cisplatin is replaced by cetuximab, a monoclonal antibody against epidermal growth factor receptor (EGFR) for chemoradiation. As cetuximab might be less harmful as compared to other treatment strategies but cisplatin is still declared as the gold standard for chemoradiation (Chew, Hay, Laskin, Wu, & Ho, 2011). Cetuximab functions as an EGFR inhibitor by attaching itself to the extracellular ligand binding region of EGFR. This allows it to effectively block endogenous ligand-activated receptors, which in turn increases cell death and decreases cell invasion, proliferation, and metastasis. The antibody-receptor complex is internalized and degraded as a result of Cetuximab binding to the receptor, which also lowers the expression of EGFR (Burtness, 2005). While on the other hand, the use of Cetuximab results in acne-like rashes, and other adverse reactions include infusion response, inconvenience, fever, nausea, loose bowels, constipation, and so on. Cetuximab, along with cisplatin, results in an increased tumor response rate from 20% to 36% (Liu, Chen, Cai, Yao, & Huang, 2019).

LESS INTRUSIVE SURGICAL APPROACH

TORS (trans-oral robotic surgery) AND TLR

Numerous options are now available for the transoral endoscopic excision of HNCs, due to advancements in instrumentation and optics. Similar approaches have been adapted for use in the oropharynx. Transoral laser techniques are commonly employed in the larynx (Wilkie et al., 2016). Improved endoscopy techniques and binocular vision capabilities contributes to precise 3D visualization. Steiner was the first to introduce an alternative philosophy through trans-oral microsurgery, which has since gained recognition in the medical community (Ashley Hay & Iain J Nixon, 2018).

Utilizing innovative and less invasive techniques like transoral robotic surgery (TORS), surgical lasers, or a combination of both, serves as the primary approach to reduce morbidity in patients with positive HPV. It is crucial to acknowledge the substantial difference between the traditional OPSCC patients group, primarily affected by tobacco and alcohol consumption, and the population driven by HPV, which tend to be younger, healthier, wealthier, more occupationally and sexually active and connected socially (Granata et al., 2012).

It should be noted that the younger patients may face extended side effects from conservative treatment after undergoing primary chemo radiation as single therapeutic choice. This could paradoxically offer them additional time to consider primary treatment again. However, traditional open surgery, frequently involving lip splitting, lateralpharyngotomy, tongue release through the floor of the mouth, or mandible splitting is not an ideal option due to the significant access-related adverse effects it causes, resulting functional and aesthetic constrains. TORS could offer a more appealing primary treatment alternative that is oncologically safe, with reduced morbidity, especially for HPV related OPSCC patients(Cohen, Weinstein, O'Malley Jr, Feldman, & Quon, 2011; Leonhardt, Quon, Abrahão, O'Malley Jr, & Weinstein, 2012)

TORS does not aim to be superior or inferior to any other surgical curative technique in the field of oncology. Rather, the difference it makes lies in the ease of surgical access and the absence of accompanying harms. One of the key benefits of TORS is making easier and reduced morbid attainment of 5 mm visible surgical margins close to a multi-planar en bloc resection in

the oral cavity, without splitting of mandible or mouth floor release. This feature not only simplifies the procedure in the range of multidimensional HNSCC therapy but also potentially reduce the need for adjuvant therapy (Weinstein, Quon, O'Malley Jr, Kim, & Cohen, 2010). Surgical mono modality can be considered in specific cases to minimize additional morbidity to a degree that may obviate the need for subsequent treatment. This can be achieved when the margin status of the primary tumor is considered alongside a dependable surgery and histopathological staging of the neck that yields a sufficient number of nodes (Ebrahimi, Zhang, Gao, & Clark, 2011; Kofler et al., 2014). The outstanding oncological results achieved by transoral laser microsurgery (TLM) and TORS can be attributed to a variety of reasons. The success of these techniques is attributed to research conducted at specific institutions and their impact on oropharyngeal conditions (De Almeida et al., 2014; Kelly, Johnson-Obaseki, Lumingu, & Corsten, 2014).

IMMUNOTHERAPUTIC APPROACH AND VACCINATION ANTIBODIES AGAINST E6 AND E7

When a foreign antigen, like a virus infection, is introduced, it may boost the immune system's ability to target the tumor. Research has indicated that humoral immune responses against viral antigens E6 and E7 are prevalent in many positive HPV cancer patients, and these responses are correlated with increased survival outcomes (Rotnáglová et al., 2011). Women with grade III intraepithelial neoplasia of vulva, who received three to four vaccinations containing lengthy proteins from HPV16 carcinogenic proteins E6 and E7, and tested HPV-16 positive, demonstrated promising results. Among the 19 patients, nine showed a complete response, while 15 presented a clinical response within a year. All patients revealed a T cell response prompted by the vaccination (Kenter et al., 2009).This enlightens the vital role of the immune system in recognizing HPV. As a result, HPV-associated HNSCC is seen as an ideal candidate for immune-based therapy (Rotnáglová et al., 2011).

GETTING RID OF IMMUNE RESISTANCE

In order for an infection to progress into cancer, immune invasion is required and to maintain the infection for an extended period. The involvement of HPV onco proteins is in facilitating this process (Näsman et al., 2013). In positive HPV-HNSCC, the PD-1, PD-L1 pathway serves as a potential mechanism for tumor immune escape. The programmed death 1 (PD-1), functioning as a T cell co inhibitory receptor, transmits inhibitory signals to the effector T cells. PD-L1 and PD-L2 are the two ligands known to bind this receptor (Brahmer et al., 2012). Furthermore, PD-1 is prominently expressed by tumor-infiltrating lymphocytes (TIL). Moreover, various studies have shown that HPV-OPC displays notable levels of PD-L1 expression, along with PD-1 expression observed in TILs (Badoual et al., 2013; Näsman et al., 2012).

The research conducted in this study has provided evidence that the interaction between PD-1 and PD-L1 establishes an immunological favored location for the first viral infection in developed tumors, resulting in the generation of adaptive immunological resistance. These findings suggest that inhibiting this pathway could offer a new approach for treating positive HPV tumors (Lyford-Pike et al., 2012). The trials involved the utilization of PD-1 and PD-L1 (Brahmer et al., 2012) antibodies to address the particular advanced malignancies in patients (Topalian et al., 2012). The main purpose of employing these antibodies was to hinder the interaction between PD-1 and PD-L1. Remarkably lasting results were observed in the PD-1 antibody trial solely among individuals with PD-L1 detected in the tumor. Consequently, further investigation into this therapeutic approach for positive HPV-OPC could be of great interest.

The earlier mentioned studies provide a rationale for investigating the use of checkpoint blocking in positive HPV-OPC across various treatment context. The primary is to improve the effectiveness of therapy in HR patients while also minimizing continued side effects through the incorporation of checkpoint inhibition into de-intensification strategies. Simultaneously, the

emergence of checkpoint inhibition and the growing interest in HPV curative vaccinations have coincided. Numerous vaccines, including those employing live vectors, peptides, genetic material, and whole cells, are developed based on the E6 and E7 early onco proteins, which are universally present in known HPV cancers (Ma, Xu, Hung, & Wu, 2010; J.-H. Su et al., 2010).

MAGE-A3 AS VACCINE

For those with head and neck cancer, immune therapies that trigger an anticancer immune reaction serve as an alternative treatment approach. A research was carried out on individuals suffering from severe HNSCC, wherein Trojan vaccinations were employed. These vaccinations were formulated peptides derived from HPV16 or HLA-I and HLA-II restricted melanoma antigen E (MAGE)-A3.

Thirteen participants with recurrent or advanced HNSCC, who turned down or were not suitable for standard treatment, were part of the study. Out of these, only five patients qualified for the trial after testing positive for MAGE-A3 or HPV-16 expression and possessing the HLA- 2 genotype.

The immunization included 300 μg of Trojan peptide enriched with granulocyte macrophage colony-stimulating factor (GM-CSF) and montanide. It was given to the patients in a maximum of four doses, spaced four weeks apart. Regrettably, none of the patients achieved full recovery. Nonetheless, four patients were able to identify the complete HLA-2 peptide and the Trojan constructs they contained (Kenter et al., 2009).

ANTI TUMOUR VACCINE

Listeria-centered vaccines serve as HPV significant and natural adjuvants, triggering a strong immune response that is both cell-mediated and specified for antigen. The antigen- adjuvant combination protein secreted by the live attenuated L. monocytogenes organism ADXS11-001 is composed of a segment of the protein listeriolysin connected to E7 of HPV (Gunn et al., 2001; Sewell et al., 2004). The investigational drug ADXS11-001 is currently being studied for individuals with HPV-positive oropharyngeal cancer who are eligible for TORS. Findings from clinical trials with cervical cancer patients suggest that vaccination therapy alone may be adequate in treating resistant HPV cancers in specific cases (Massarelli, Ferrarotto, & Glisson, 2015).

Considering the newly available evidence on the widespread suppression of, both broad and specific to HPV, that occurs after treatment, a viable option is to integrate immunotherapy with definitive connected chemo RT. By combining these two approaches, we can capitalize on their synergistic effects and potentially improve patient outcomes (Parikh et al., 2014).

MOLECUALR THERAPY TARGETING FGFR

Evidence from preclinical studies suggests that targeting FGFR signaling may be a promising approach in HNSCC, and like PI3K, there is proof that EGFR activation could provide protection (Wu et al., 2013). Ongoing phase I trials as NCT01962532, are currently investigating the use of FGFR inhibitors (Massarelli et al., 2015). It is anticipated that these trials will assess the efficacy of FGFR inhibitors in definite molecular subsets of HNSCC, including somatic mutations in FGFR related molecules and FGFR over expression.

USE OF VELIPARIB

DNA repairing proteins, like PARP (poly-ADP ribose polymerase) are upregulated; changes in DNA repair gene exist; and p53 and pRb are downregulated in HPV-related OPC, giving reasoning to examination of PARP inhibitors and inhibitors of the DNA damage checkpoint kinases (Chk1/2) (Byers et al., 2014). PARP might be prognostic for reaction to single-agent veliparib, a PARP inhibitor, and that PARP inhibition joined with either cetuximab or radiation improved cytotoxicity, compared with veliparib alone, through inhibition of DNA repair. Due to myelosuppression observed with PARP inhibitors and chemotherapy, along with cetuximab and radiation, this might demonstrate more achievable in HPV-related OPC (Nowsheen et al., 2011).

ROLE OF CHECK-POINT KINASE

The Chk1/2 kinases assume a basic part in genomic observations and might be especially significant in interceding cell-cycle arrest in light of DNA damage when typical p53 is missing. Inhibition of Chk1/2 turned around cisplatin resistance, mediated by the absence of active p53, causing mitotic cell demise in negative HPV- HNSCC cell lines. In the light of the downregulation of p53, expecting this would be a successful system for HPV+ OPC also (Gadhikar et al., 2013).

Wee-1 kinase inactivates cyclin-dependent kinase, permitting DNA damage caused by G2-M arrest. Studies support that Wee-1 improves the impacts of cisplatin and radiation in HPV+ HNSCC cell lines. Outstandingly, this impact was related with upgraded apoptosis interceded by the diminished expression of other protein and is distinct in mechanism of cisplatin sensitization of HPV cell lines (Zolkind et al., 2017)

PK13

Early observations suggest that HNSCC cell lines having PIK3CA-mutation display resistance to EGFR inhibitors, underscoring the potential benefits of combining them with cetuximab. In HPV+ OPC, the PI3K pathway is activated in 50% of cases(Young et al., 2013). The effectiveness of PI3K inhibitors appears to be limited to individuals with solid tumours containing PI3K− mutations, suggesting that a combination of therapies is more favorable in initial clinical studies (Holsinger et al., 2013; Janku et al., 2011; Lui et al., 2013; Mazumdar et al., 2014). Two phase II trials, conducted randomly, have investigated the efficacy of PX866, PK13 antagonist pan class 1, when combined with either cetuximab or docetaxel. However, neither trial demonstrated any favorable impacts in clinical effectiveness measures (Jimeno, Bauman, et al., 2015; Jimeno, Shirai, et al., 2015).

CONCLUSION

The reviewed studies explore the etiology, transmission pathways, molecular mechanisms, genomic structure, and a range of treatment strategies for HPV-associated cancers. Targeted therapies have shown promise by offering specificity in cancer treatment, thereby minimizing host toxicity and enhancing patient quality of life. Despite challenges such as drug resistance, the integration of targeted therapies with radiotherapy, chemotherapy, or multi-targeted approaches presents a viable path forward. Furthermore, immunotherapies including antibody-based treatments and vaccines targeting HPV are gaining attention for their ability to provoke strong anti-tumor responses. Advances in molecular therapies and non-invasive surgical techniques, especially when combined with systemic treatments, have also shown encouraging outcomes. Moving forward, achieving optimal oncological results with reduced morbidity in patients with oropharyngeal squamous cell carcinoma (OPSCC) will require continued research and clinical trials focused on refining chemoradiotherapy, molecular-based treatments, immunotherapies, and minimally invasive surgical strategies.

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