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Review article

Monoclonal Antibodies as Treatment Modalities in Head and Neck Cancers

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Abstract: The standard treatments of surgery, radiation, and chemotherapy in head and neck squamous cell carcinomas (HNSCC) causes disturbance to normal surrounding tissues, systemic toxicities and functional problems with eating, speaking, and breathing. With early detection, many of these cancers can be effectively treated, but treatment should also focus on retaining the function of the proximal nerves, tissues and vasculature surrounding the tumor. With current research focused on understanding pathogenesis of these cancers in a molecular level, targeted therapy using monoclonal antibodies (MoAbs), can be modified and directed towards tumor genes, proteins and signal pathways with the potential to reduce unfavorable side effects of current treatments. This review will highlight the current MoAb therapies used in HNSCC, and discuss ongoing research efforts to develop novel treatment agents with potential to improve efficacy, increase overall survival (OS) rates and reduce toxicities.

Keywords: monoclonal antibodies; hnscc, cetuximab; cisplatin; tumor antigens; immunotherapy; genome sequencing; HPV tumors

1. Introduction

Head and neck cancer accounts for about 3% of all cancers in the United States. This year, approximately 45,000 people will develop head and neck cancer with an estimated 8,000 deaths [1]. HNSCC is the most frequent malignant tumor that arises from the mucosal linings of the mixed airway/gastrointestinal tract which includes the oral cavity, pharynx, paranasal sinuses, sinonasal tract, larynx, pyriform sinus and upper esophagus. The incidence of HNSCC has slowly decreased in the past few decades, mainly due to the drop off in smoking. Nonetheless, certain HNSCCs of the oropharynx and oral cavity are increasing in prevalence due to a rise in sexually transmitted Human Papilloma Virus (HPV) infections [2]. Currently, treatment options include surgical resection, chemotherapy, radiation, and most recently, limited targeted molecular therapy [3]. The correlation found between elevated expression of epidermal growth factor receptor (EGFR) in HNSCCs with suboptimal survival outcomes [4–6] provided researchers with one of the first and most studied molecular targets in HNSCCs over the years. With recent advancements in genomic technology, the discovery of new antigens might shed light in developing novel treatment agents that could reduce toxicities, and improve survival outcomes.

2. Emergence of Passive Immunotherapy

The main approaches in biological immunotherapy are active and passive therapy. While active therapy works by prompting the host to build up its own immune response (vaccines), passive therapy engages the use of pretreated immune globulins, created ex vivo, and introduced as targeted therapy [16]. The immune response is the result of tightly organized relationship among antigen presenting cells, T lymphocytes and target cells. The initial step requires the identification of antigen peptides bound to major histocompatibility complex (MHC) on T cell receptors, leading to ligation of CD28 protein and activation of signaling pathways resulting in T cell activation with interleukin (IL-2) production [18]. This activation of T cells causes the translocation of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) an important regulator, from within the cell to the cell surface, where its high affinity to the same B7 (peripheral membrane protein) molecules that engages with T cells, leads to disruption of the signaling cascade mediated by CD28, thus halting the progression of an immune response [17]. This concept lead to development of Ipilimumab and Tremelimumab, two MoAbs capable of blocking CTLA-4 and potentiating T cell activation to trigger responses on cancer cells [19]. Following a phase III trial, the FDA approval of Ipilimumab became one of the first treatments to show significant OS improvement in metastatic melanoma patients [20]. Albeit, CTLA-4 inhibition showed great promise, it also unearthed unfortunate inflammatory responses mostly in the skin and gastrointestinal tract. To counteract these side effects, corticosteroids were added to the treatment regimen, but the outcome relied heavily upon early diagnosis of the cancer [20].

The promising results shown with Ipilimumab has created a frenzy of curiosity among researchers to identity other targets that might provide better outcomes and possibly less severe side

effects. Some of these receptors include 4-1BB, OX40, GITR, CD27 and CD28 among many others [17]. One approach deals with triggering of tumor cell apoptosis by targeting programmed cell death protein 1(PD-1), which is expressed by activated T cells and binds to programmed cell death ligand 1/ligand 2 (PD-L1/L2) [22,23]. PD-L1 expression has been shown to correlate with poor prognosis and increased activation of oncogenic phosphatidylinositol 3-kinase (PI3K) pathway [24–26]. Early clinical trials of PD-1 inhibition has demonstrated good activity and positive responses in patients with a wide array of tumors, including melanoma, renal cell carcinoma, non-small cell lung cancer and colorectal cancer [27]. The toxicity of PD-1 antibody in these trials appear to be far less severe compared to Ipilimumab [22].

To date, the FDA has approved several antibodies for treatment in patients with a multitude of solid tumors. Their target antigens and mechanisms of actions vary accordingly. Trastuzumab (Herceptin), Cetuximab (Erbitux), Panitumumab (Vectibix) and Bevacizumab (Avastin) are humanized IgGs that target ErbB (epidermal growth factor) family and vascular endothelial growth factor (VEGF) [28–33]. These have shown success in patients treated for ERBB2—positive breast, gastro and gastro-esophageal junction carcinomas, when used as a single agent or in combination with cisplatin [18]. Other agents such as Catumaxomab an antibody against CD3 protein complex and epithelial cell adhesion molecule (EpCAM) [34] and Nimotuzumab an IgG antibody against epidermal growth factor receptor (EGFR) have been approved in countries outside of U.S. for treating head and neck cancer, glioma and nasopharyngeal cancer [35]. Despite the fact many tumor specific antigens having been identified, only a handful are exclusive to HNSCC.

3. Cetuximab as Standard of Care

The complex nature of HNSCC requires an integrative treatment approach. Early tumors can be treated with single modality therapy with surgery or radiation, while advanced stage tumors require multimodal treatment, which may include chemotherapy. The possibility of recurrence or metastases remains high despite this aggressive multimodality approach. Cetuximab, a monoclonal antibody of immunoglobulin G1 class (IgG1), received Food and Drug Administration (FDA) approval in 2006, after a phase III trial exhibited a survival benefit amongst patients with HNSCC when accompanied with radiation therapy (RT) [7]. Cetuximab hinders the up-regulation of EGFR by disrupting its binding to autocrine ligand [8–10]. It also initiates cell-mediated cytotoxicity [11–13] as well as augmenting and improving the effect of cisplatin and other chemotherapy agents. Numerous studies have been done to determine the efficacy of cetuximab as a single agent or in combination with RT or cisplatin-based chemoradiation (CRT) in locally advanced disease. In a study conducted by Bonner et al, cetuximab with RT improved the 5-year (OS) rate by approximately 10% compared to RT alone [7,36–37]. However, data from several retrospective studies, Pryor et al, Shapiro et al, Chew et al and Koutcher et al showed increased toxicity, more pronounced oral and skin lesions, loss of weight and higher incidence of feeding tube placements associated with the addition of cetuximab [38–41].

In recurrent or metastatic HNSCCs, studies like the randomized trial by Vermorken et al showed cetuximab plus CRT prolonged OS and response rates when compared to CRT alone. Similar results were observed by Hitt et al with the combined use of paclitaxel (taxane) and cetuximab [42–43].

The combination of cetuximab and CRT however viable, showed no significant difference compared to CRT alone in locally advanced disease. As seen in the Radiation Therapy Oncology Group (RTOG) trial, the 2-year OS was 82.6% in CRT and cetuximab group and 79.7% in CRT treated group. The relapse rate was higher in cetuximab containing group by approximately 5%. In addition, the study also showed increased mucositis and dermatitis associated with cetuximab group [44]. Another retrospective study by Ley et al, showed disease-free survival (DFS) of 79% in CRT group versus 27% in cetuximab treated group and OS of 72% vs 25% respectively [45]. Until evidence from a phase III randomized trial comparing CRT versus cetuximab shows significant OS benefit, CRT remains standard of care. A RTOG 10-16 clinical trial is currently under way which addresses this issue. The trial which is expected to conclude in June 2020 focuses on a direct comparison between cetuximab and CRT in HPV—positive oropharyngeal cancer. Several other trials of MoAbs specific to HNSCC are ongoing (Table 1).

4. Promising Antigens in Head and Neck Cancers

Over the past decade, tremendous attention has been paid to developing and perfecting treatments targeting the EGFR signaling pathway. In recent years however newer antigens targets have been identified that have shown successful outcomes in non HNSCC malignancies. Efforts are focused now to see if similar results can be duplicated in HNSCC using the same antigen targets (Table 2).

In nearly 80% of HNSCC the identification of mutated phosphoprotein (p53) makes it one of the most expressed tumor associated antigens [46]. The mutation is associated with a structural modification of a protein that fails to breakdown easily and leads to a build-up of p53 proteins. The accumulated p53 provides a platform for tumor vaccine development [16]. The identification of histocompatibility leukocyte antigen (HLA)-A1 among a myriad of other p53 specific epitopes [47,48] showed increased p53 specific T cell immune response. Further studies showed smoking [51] with the synergism of mutated p53 and p73 genes augmented the possibility of developing HNSCC [52]. Tumor remission was witnessed by Clayman et al. in approximately 50% of patients with HNSCC who were given p53-transfected adenovirus [53].

As previously discussed, many melanoma associated antigens (CTLA-4, PDL1) can also be seen in HNSCC cells [49–51]. The clinical trials by Edelman et al. which started in 2008 on HNSCC patients focuses on the melanoma associated antigen (MAGE-3) and human papilloma virus (HPV) following the results of a successful phase III vaccination trial of non-small-cell lung cancer that targeted MAGE-3. The likelihood of success in using HPV-specific therapy was also shown to be promising in preclinical studies where a tumor specific immune response was observed in HPV-positive

HNSCC patients [54,55]. The recent discovery of genomic differences in cancers caused by HPV infection by The Cancer Genome Atlas Research Network (TCGA) has shed new light in the pathogenesis of head and neck cancer and potential diagnostic and treatment targets. The identification of mutations in the oncogene Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha (PIK3CA), loss of TNF receptor-associated factor 3 (TRAF3), and amplification of cell cycle gene E2F1 are expressed vigorously in HPV associated tumors [56].

The strong implication that mammalian target of rapamycin (mTOR) a downstream signal of phosphatidylinositol-3-kinase PI3K/AKT/mTOR signaling pathway, in the development of HNSCC [57,58] was suggested almost a decade ago. mTOR is activated by Akt that leads to prevention of apoptosis and unrestricted cancer cell propagation. Studies show high levels of mTOR protein expression was a prognostic marker of recurrence in patients with laryngeal carcinoma treated with postoperative radiotherapy [59]. While evidence exists that show the use of mTOR inhibitors (rapamycin, temsirolimus, everolimus, and ridaforolimus) on head and neck cancer cells in xenografts and in-vitro cell lines demonstrated inhibition of mTOR signaling pathway, results from ongoing clinical trials are yet to be published. Another attractive aspect of mTOR inhibitors is its possible augmented action while combined with other treatment modalities (radiation, chemotherapy, targeted agents).

5. Limitations of Monoclonal Antibodies

The history and concept of MoAbs as cancer immunotherapy spans decades of research and clinical trials, but the threshold of a successful treatment has yet to be met. While the concept of immune therapy sounds simple, several limitations exist. One simple limitation could be that MoAbs are usually given to patients who have been through initial treatment options of surgery, radiation and chemotherapy leaving behind an exhausted immune system and the effectiveness of MoAbs become inefficacious. We also have to take into account that not all antigens are the same. Although the clinical presentation and manifestation of cancers among various patients might be identical, the antigen presented by these cancer cells may vary, and hence one MoAb is tolerated and effective in one patient population, it's rendered ineffective in another. Many cancer cells will eventually learn to adapt via mutations, leading to reduced affinity and efficacy of MoAbs. The use of molecular genomics and advancement in technology might enable researchers to identify a subgroup of patients with a specific cancer and tailor a therapy on an individual basis.

As previously discussed, with the use of Ipilimumab, there were significant toxicities observed [17]. Among the patients treated with Ipilimumab, approximately 23% had developed colitis and hypophysitis most likely due to an autoimmune response. Increased liver function tests (LFT) in 10% of patients when treated in combination with Dacarbazine were also noted [17]. An inflammatory response can be demonstrated by many patients undergoing treatment, but the drawback is not knowing if any effect is undertaken on the cancer cells, because no correlation exists between the levels of toxicity and positive therapeutic outcome [17]. Another shortcoming is delayed treatment

effect compared to standard therapies. The traditional treatments of chemo-radiation therapy will show a rapid clinical response resulting in reduction of tumor size and volume within weeks to months. However, responses seen using targeted immune therapy may be delayed or sometimes even preceded by an increase in tumor size. With the use of Ipilimumab, long term tumor control or regression was seen but an initial increase in tumor size occurred approximately 3 months after treatment initiation. The reason behind this delayed response is still under investigation, but it could be due to the prolonged time T cells need to prepare an immune response [17].

6. Genomic Sequencing of HNSCCs

The identification of gene variants using next-generation sequencing allows scientists to use cell fusion and recombinant DNA techniques to synthesize, isolate and produce antibodies to target specific antigens.

The findings of the National Institute of Health (NIH) funded study to find and compile a comprehensive list of genomic alterations in HNSCCs was published earlier this year (January 2015). The investigators were part of The Cancer Genome Atlas (TCGA) Research Network in an effort to understand the roles of HPV and smoking in development of head and neck cancers. The reported data consists of a complete data analysis of 279 patient profiles of untreated head and neck cancers which has led to constructing a detailed blueprint of genomic variants in HNSCC. As discussed earlier, mutations of the oncogene PIK3CA, loss of TRAF3, and amplified cell cycle gene E2F1 are shown to be associated strongly with HPV (+) tumors. TRAF3s role in regulating type I interferons makes it an indispensable component against viruses including Epstein-Barr, HIV and HPV [6–9] and its loss leads to activation of NF-kB pathway leading to expression of pro inflammatory genes (cytokines) [10]. While TRAF3 inactivation has been identified in other malignancies [11,12] this recent data shows its association with HPV related oropharyngeal cancers.

The researchers also report similar gene actions in HPV (−) HNSCCs. The amplification of certain genes (CCND1, FADD, BIRC2 and YAP1) or mutations in others like CASP8 (Apoptosis-Related Cysteine Peptidase) maybe the key in production of treatment resistant cells due to their role in regulating cell cycle and death. The study also reported several gene mutations leading to unfinished protein products, among which, AJUBA a centrosomal protein regulating cell death (23), and FAT1 (FAT Atypical Cadherin 1) genes causing their inactivation and unimpeded cell differentiation. While certain gene alterations are specific to HPV (+) cancers, gene alterations in FGFR3 (fibroblast growth factor receptor 3) and PIK3CA have also been found in smoking-related tumors. Such pertinent findings provide much needed understanding of the disease process in HNSCC and can open up new alleys in development of targeted treatments and preventing disease progression.

7. Discussion

HNSCC is a highly complex cancer and the development and use of MoAbs in treating these cancers has exciting potential. Understanding the behavior of cancer cells, identifying target antigens, and detailing immune system pathways have allowed scientists to explore new approaches in antibody therapies. With decades long work this concept of manipulating the immune system to treat patients with cancer is now in the age of fruition.

With the clinical success of Ipilimumab in metastatic melanoma patients, it has paved the way for use of Cetuximab in treating HNSCCs. Currently, several phase III trials are being conducted using antibodies against several types of cancers and the results of these studies may provide additional treatment options for HNSCC patients. With the implementation of genomic analysis to identify mutant variants, the data has been extremely crucial and has allowed for a deeper understanding of HNSCC pathology. While certain genomic mutations are unique to HPV (+) and HPV (−) HNSCCs, the discovery of shared alterations with other cancers may provide a new direction in treatment development which could theoretically minimize adverse effects, monitor treatment response and prolong survival.

Conflict of Interest

The authors have no conflict of interest.

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Table 1. Ongoing trials of monoclonal antibodies (MoAbs) in HNSCC treatment.

Antibody	Mechanism	Trial (Identifier)	Study Status
MEHD7945A	Anti-HER3/EGFR	Phase 1 study of MEHD7945A in combination with cisplatin and 5-FU or Paclitaxel and Carboplatin in patients with recurrent/metastatic HNSCC. (NCT01911598)	Estimated completion date: May 2016
		Phase 2 study of MEHD7945A versus Cetuximab in patients with recurrent/metastatic HNSCC (NCT01577173)	Estimated completion date: November 2015
Nimotuzumab	Humanized IgG1 MoAb directed at EGFR	Phase 2 study of Nimotuzumab and Cisplatin/Radiotherapy for Locally Advanced Head and Neck Squamous Cell Cancer (NCT00702481)	Estimated completion date: December 2016
Bevacizumab	Anti-VEGF	Phase 3 study of Chemotherapy with or without Bevacizumab in treating patients with recurrent or metastatic head and neck cancer (NCT00588770)	Estimated completion date: December 2017
Pembrolizumab	Anti- PD1	Phase 3 study of Pembrolizumab versus standard treatment for recurrent or metastatic head and neck cancer (NCT02252042)	Estimated completion date: April 2017
		Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (NCT02358031)	
Durvalumab (MEDI4736)	Anti- PD-L1	Phase I Study to Evaluate the Safety, Tolerability, and Efficacy of MEDI4736 in Combination with Tremelimumab in Subjects with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (NCT02262741)	Estimated completion date: January 2017

Abbreviations: HNSCC, Head and Neck Squamous Cell Carcinoma; HER3/EGFR, Human Epidermal Growth Factor Receptor Type 3/Epidermal Growth Factor Receptor; HER2/EGFR, Human Epidermal Growth Factor Receptor Type 2/Epidermal Growth Factor Receptor; 5-FU, fluorouracil; IgG1, Immunoglobulin; VEGF, Vascular Endothelial Growth Factor; PD-1, Programmed Cell Death Protein-1; PD-L1, Programmed Death Ligand 1. (Source: www.clinicaltrials.gov)

Table 2. Current studies of tumor specific antigens.

Target	p53	PI3K	Aurora Kinase A	NY-ESO-1	HPV	mTOR
Trial (Identifier)	Phase 2 trial of p53 Gene Combined with Radio- and Chemo-therapy in Treatment of Unresectable Locally Advanced Head and Neck Cancer (NCT02429037)	A Phase Ib/II Study of BYL719 (PI3K inhibitor) and Cetuximab in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (NCT01602315)	Phase I Study of Aurora A Kinase Inhibitor (MLN8237) Given in Combination With Selective VEGFR Inhibitor Pazopanib (Votrient) for Therapy in Solid Tumors (NCT01639911)	Phase I Study of Malignancies That Express NY-ESO-1 With T Cell Receptor-transduced T Cells Targeting NY-ESO-1 (NCT0245765)	Pilot 2-Part Prospective Study of HPV Specific Immunotherapy in Patients With HPV Associated Head and Neck Squamous Cell Carcinoma (HNSCC) (NCT02163057)	Rapamycin Therapy in Head and Neck Squamous Cell Carcinoma (NCT01195922)
Status	Estimated completion date: December 2018	Currently recruiting patients. Estimated completion date: December 2016	Currently recruiting patients. Estimated completion date: September 2015	Currently recruiting patients. Estimated completion date: December 2019	Currently recruiting patients. Estimated completion date: June 2017	Estimated completion-n date: June 2016

Abbreviations: p53, phosphoprotein; PI3K phosphatidylinositide-3-kinases; VEGFR, Vascular Endothelial Growth Factor Receptor; HPV, Human Papilloma Virus; NY-ESO-1, Auto immunogenic cancer/testis antigen; mTOR, mechanistic target of rapamycin (Source: www.clinicaltrials.gov)