Review article

Advancements in Targeted Molecular Therapy for Human Papillomavirus (HPV) Related Cancer

Amanda Szymanski[1,2*], Joel E. Mortensen[1,3], Patricia Tille[1]

Medical Laboratory Sciences Program, College of Allied Health Science, University of Cincinnati, Cincinnati, Ohio[1]
ICON plc, Whitesboro, New York[2]
Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio[3]

Human papillomavirus (HPV) is a common sexually transmitted disease among both men and women. High risk cases can quickly develop into cancer, most frequently in the cervix and oropharynx. Standard treatment options include surgery and chemotherapy both of which are painful, hard on the body, and can leave the patient with long term side effects. Unlike traditional therapy methods, molecular targeted therapy focuses specifically on molecular changes making it more effective, highly specific, and more tolerable than more traditional methods. Molecular targeted therapy has shown promising results for various types of cancer. Recent developments for HPV specific cases have led to some exciting advancements in precision medicine.

Cetuximab and gefitinib are two recently developed molecular targeted therapy drugs that target epidermal growth factor receptors (EGFR) to deactivate molecular pathways responsible for cancer growth. Both drugs are proven to be safe and effective therapy options that can improve the patient's overall survival and decrease disease recurrence. However, drug resistance remains problematic for patients using molecular targeted therapy. A common solution is combining molecular targeted therapy with additional options such as chemotherapy or other targeted therapies. This has the potential to eliminate drug resistance. However, there are limited target therapies available for HPV cancer. This demonstrates the need for further research and drug development for HPV related cancer cases to make further advancements.

Key words: Human papilloma virus; Cancer; Molecular targeted therapy; Molecular target identification; Oropharyngeal; Molecular detection; miRNAs; Epidermal growth factor signaling; Kinase inhibitors; Monoclonal antibodies; Cetuximab; Gefitinib; Resistance; T790M

Introduction

Human papillomavirus (HPV) is a viral infection that is primarily sexually transmitted and can lead to HPV-related cancers in both men and women. It is currently the most common sexually transmitted infection in the United States.[1] High risk HPV infections are the cause for all cases of cervical cancer and some cases of oropharyngeal cancer.[2] The HPV-16 subtype accounts for approximately 95% of HPV-positive cases of oropharyngeal cancer and subtypes HPV-16 and HPV-18 are responsible for up to 70% of the cases of cervical cancer.[3] Less

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*Corresponding author: Amanda Szymanski. Email: szymanaa@mail.uc.edu

frequent HPV genotypes that also contribute towards the development of cancer include 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82.[3] In addition, HPV is associated with multiple noncervical malignancies. These can include vulvar, vaginal, penile, anal, esophageal, and head and neck cancers.[2] The number of head and neck cancers linked to HPV, especially oropharyngeal cancer, has been progressively increasing.[1]

Cervical cancer is the most common HPV-related disease and cancer in women. HPV is classified as a sexually transmitted disease. However, it has been reported that skin-to-skin contact can be efficient enough to facilitate viral transmission. HPV is associated with a variety of clinical conditions including lesions, warts and occasionally cancer.[6] Almost 80% of males and females will test positive for an HPV infection at some point in their lifetime.[1] Many low-risk HPV infections are benign and cause lesions such as cutaneous warts on the hands, feet and anogenital regions.[4] Typically, the immune system will clear the virus, however in some cases the infection can progress into high-risk HPV and lead to precancerous changes or tumors.[1,4] The virus infects the mucocutaneous epithelium and produces viral particles in matured epithelial cells. This causes a disruption in normal cell-cycle control. The promotion of uncontrolled cell division can then lead to genetic damage.[4]

Oropharyngeal cancers have been linked to tobacco and alcohol consumption. However, recent studies show that about 70% of cancers of the oropharynx are linked to HPV infection.[1,3] Over the past 20 years in the United States, the detection of HPV related oropharyngeal tumors has increased from 16% to 73%. The oropharynx has become the most common site of HPV-related cancer, surpassing the cervix. Male predominance is evident in HPV related oropharyngeal cancer with a male-to-female ratio of about 4:1. This may correlate with a higher prevalence of oral HPV-16 infections in men opposed to women.[3] Recent studies have also investigated the differences in HPV genotype distribution in comparison to age. It was shown that there is a higher level of HPV in younger HPV-positive oropharynx cancer patients in comparison to older patients. HPV positivity in oropharynx cancer depends on the intensity of sexual exposure, explaining the lower numbers of HPV positive cancers in older patients. The reduced use of alcohol and tobacco has decreased the number of oropharynx cancer cases however, the HPV infection-related cases have begun to increase.[1]

As HPV infection has become more notable in oropharyngeal cases as well as cervical cancer, it is important that treatment options improve. Standard treatment options for patients diagnosed with HPV related cancer include surgery, chemotherapy, and local radiation therapy.[2] Patients diagnosed with cancer in the early-stages are generally treated with radiotherapy or surgery while more advanced cancer is treated with a combination of surgery and either radiotherapy or chemoradiation.[5] HPV related cervical cancer patients are often treated with radiation therapy, although some patients will require a full hysterectomy to remove the cancer.[3] However, recurrent and metastatic disease remains one of the main causes of mortality in HPV related cervical cancer.[2] Patients with early stages of HPV related oropharyngeal cancer can also be treated with surgery and radiation therapy. However, many patients with oropharyngeal cancer are not diagnosed until the cancer has reached an advanced stage. Therefore, harsher treatments are required which includes a combination of chemoradiation and surgery followed by several treatments of radiotherapy.[3] These standard treatments are often successful in eliminating cancer, however they are extremely toxic and damage other tissues and muscles in the surrounding organs. These severe side effects have led scientists to conclude that the current standard of care is over-treating patients. By restructuring some of the treatments it might be possible to achieve

comparable survival outcomes while simultaneously lowering toxicities and reducing the need for invasive surgical procedures.[5]

As new findings and approaches in molecular biology have become available, advancements in molecular targeted therapies have become an option for treating patients with HPV related cancer and are not associated with the negative long-term side effects.[5] Molecular targeted therapy is the use of drugs or other substances that target specific molecules to block the growth and spread of cancerous cells. Selecting the appropriate molecular target is essential for successful treatment. Food and Drug Administration (FDA) approved molecular target therapies have been successful in the treatment of various types of cancer.[6]

Limitations associated with targeted molecular therapy for the treatment of cancer includes the specificity of the biomarkers, and the need for a better understanding of how to implement this technology in treatment regimens.[5,6] The success of molecular targeted therapy is dependent on a patient's tumor expression of the specific biomarker used as the molecular target. Different genetic mutations occur that can be linked directly to the development of cancer. Therefore, identifying the molecular target for successful treatment can be difficult.[6] Currently, there are very few molecular target treatment methods available that are FDA-approved. This is partially due to the methods not pairing well with patients undergoing radiation. A better understanding of the biology behind HPV related cancer is needed to design newer therapeutic strategies. Targeted therapies must be safe and demonstrate an improvement in patient outcomes in comparison to the available standard treatment options such as surgery, radiotherapy or chemoradiation.[5]

Molecular targets

To develop molecular targeted therapies, it is important to consider what type of molecules may be useful for further analysis and consideration for the treatment of HPV related cancer. Growth factors, signaling molecules, cell-cycle proteins, apoptosis modulators and molecules that promote the development of new blood vessels are potential therapeutic molecular targets.[6] Molecular signaling pathways involved in the deregulation of critical molecular processes are also an option for use as a molecular target.[2] There are several items to consider when choosing a molecular target. Not every molecule in a cancer cell has the potential to be used as a target. Molecules that have been identified to function as useful targets are often embedded in the outer membranes of tumor cells. The cell membrane molecules tend to bind to therapeutic drugs and are effective molecular targets.[7]

Molecular Targets in Drug Development

Therapeutic drugs, oral or injectable, can be designed to effectively bind molecular targets present in cancer cells responsible for promoting tumor growth. The drugs can be used to prevent the formation of new blood vessels cutting off the nutrient and oxygen supply to the tumor cells resulting in cell death.[6]

In addition to the preferred location of a target molecule in the cell membrane of a tumor, a target molecule should also be present in many of the patients with a specific tumor type. The target molecule should not be present in normal tissue, otherwise use of the target may result in toxic side effects to the patient. It is also important to determine if the target molecule is associated with resistance to apoptosis, uncontrolled cell proliferation, increased cell migration, altered cellular adhesiveness, or modulation of the immune response.[7] If the molecule is not associated with toxicity or other cellular functions as noted it can then be considered a potential molecular target for therapy.

HPV Molecular Targets

Various molecules have been identified as targets for HPV treatments. The early (E) HPV proteins E1, E2, E4, E5, E6, and E7 are necessary for viral integration, replication and

transcription. E6 and E7 are considered oncoproteins and are responsible for cell proliferative signaling, deregulating cellular energies, and avoiding growth suppressors. While the primary role of the E5 protein is to avoid immune destruction. HPV E5, E6, and E7 oncoproteins are capable of altering the functions of multiple signaling pathways and inducing cervical cancer.[2] Viral E6 and E7 oncoproteins alter transcriptional control. Therefore, detection of the abundant expression of HPV *E6/E7* transcripts can be used to predict underlying cervical precancer. This correlates to the presence of high-risk HPV (HR-HPV) rather than simply viral presence.[8] E6 targets the tumor suppressor protein p53 by forming a complex with the E3 ubiquitin-protein ligase E6-associated protein (E6AP) promoting proteasomal degradation. The viral protein complex can also block transcription of the tumor-suppressor. The degradation of the p53 protein promotes viral replication leading to the accumulation of genetic mutations that result in host cellular transformation, dysplasia, and cancer.[9]

E6 and E7 also play a role in oropharyngeal HPV-related cancer. Oropharyngeal HPV-related tumors occur around the tonsils, base of the tongue and soft palate. The cancerous tumors develop when viral oncoproteins E6 and E7 are overexpressed and promote tumor progression by inactivating the *TP53* and retinoblastoma tumor suppressor genes. E7 will bind to the retinoblastoma *protein (Rb),* which will disrupt the cell cycle and initiate transcription of S-phase genes.[8] This will then stimulate the phosphoinositide 3-kinase (PI3K), protein kinase B (Akt) pathway which is a main cancer survival pathway involved in signal transduction.[2] The tumor suppressor proteins, p16 and Rb help regulate the G1 and S phase of the cell cycle. When HPV infection causes cancer, Rb becomes functionally absent and p16 is overexpressed due to the loss of negative feedback.[8] When AKT becomes phosphorylated it can lead to increased tumor progression, and drug resistance. This makes an oncogene mediated pathway such as (*PI3K*)/(*Akt*) a promising molecular target.[2]

Another potential target for both cervical and oropharyngeal cancer is micro ribonucleic acids (miRNAs). The miRNAs are small non-protein coding human RNAs that are about 18-25 nucleotides in length involved in the regulation of gene expression and messenger RNA (mRNA) translation and decay.[2,10] Human miRNAs are also involved in the regulation of cell growth, apoptosis, cell migration, and metastasis. miRNAs may be useful as biomarkers for the detection of several types of cancers including HPV. A single miRNA can alter the expression of hundreds of genes. This makes the identification of the change in expression of a specific or multiple miRNA's associated with cancer as potential targets for use in diagnostics and therapeutics.[2] The miRNA patterns are also tissue-specific which makes it easy to distinguish carcinomas from normal cells.[10]

Advancements in HPV therapy

HPV targeted molecular therapy uses agents such as tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAB) to block the growth of malignant cells by interfering with the essential pathways needed for the development of tumors.[11,12] TKIs are small molecular weight drugs that are orally administered. A TKI will bind a targeted sites to induce molecular changes that inhibit kinase enzyme activity. A mAB is administered via injection since the molecular size of the antibody is too large to penetrate cellular membranes. The antibodies interfere with signal transduction from the cell surface and provoke apoptosis or interfere with protein functions needed for the growth of cancer cells.[12] Targeted molecular therapies may use mABs and TKIs to target epidermal growth factor receptors (EGFR). EGFR receptors contribute to disease progression and therapy resistance in a variety of human cancers.[7]

Epidermal growth factor receptors are transmembrane glycoproteins responsible for

the regulation of cell growth and proliferation.[13] The presence of an HPV infection causes an upregulation of EGFR signaling and contributes to the progression of cancer in the cervix and oropharynx.[11] Most HPV related cancers over express EGFR on the surface of tumor cells making it a good target for molecular therapy.[14]

Advancements in molecular targeted therapy for HPV patients includes the use of the therapeutic drugs cetuximab and gefitinib. These drugs have shown promising results in clinical trials by successfully reducing tumor activity in HPV patients. Cetuximab uses mABs to bind to the extracellular domain of EGFR while gefitinib uses TKIs to bind to the intracellular kinase domain of EGFR.[14]

Cetuximab

Cetuximab is the only FDA approved targeted therapy proven to increase the overall survival of HPV related head and neck squamous cell carcinomas (HNSCC) in combination with radiotherapy.[14] Cetuximab is an injected monoclonal antibody used for oropharyngeal cancer that targets EGFR. It is also the only drug proven to treat both recurrent cancer and cancer restricted to a localized region of the body.[13,14] Cetuximab binds to the extracellular domain of the EGFR and blocks the activation of the protein receptor's intracellular domain interfering with the associated tyrosine kinase-dependent signal transduction pathway. This results in the internalization of EGFR removing the receptor from the cell surface and prevents any interaction with the protein ligands.[13] Cetuximab effectively alters the cell surface membrane structure which initiates apoptosis of tumor cells by activating natural killer (NK) cells and inducing antibody dependent cellular cytotoxicity.[11]

In addition to blocking EGFR, cetuximab blocks cellular secondary repair mechanisms dependent on the *PI3K/Akt* pathway mitogen-activated protein kinase **(**MAPK), and Janus kinase/ signal transducer and activator of transcription of the (*JAK/STAT3*) downstream signaling pathway. This causes a reduction in the capacity of the cellular DNA repair as well as decreasing the number of cells entering the S phase of the cell cycle.[13]

Clinical trials have begun testing cetuximab on cervical cancer in human cell and animal models. These studies have demonstrated a decrease in tumor activity as well as an increased production of cluster of differentiation 3 positive thymus cells (CD3 + T cells), CD8 + T cells and NK cells. The increase in the population of immune cells indicates that cetuximab effectively improved immune function and reduces tumor activity.[11,13] These results are promising for the future of cetuximab therapy specifically related to cervical cancer.

Gefitinib

Gefitinib is an orally administered therapeutic drug that prevents phosphorylation and tyrosine kinase activity of the intracellular domain of EGFR. Gefitinib is FDA approved for the treatment of lung cancer. Numerous clinical trials have begun testing the clinical efficacy of gefitinib on various cancers including HPV related cervical cancer.[15,16] Gefitinib is a TKI that targets EGFR. Patients treated with gefitinib have shown signs of improvement and tumor regression in non-cell small lung cancer.[15] Gefitinib binds EGFR and blocks the canonical wingless/integrated Wnt/ß-catenin signaling pathway that is involved in the regulation of cell polarity and migration. The Wnt/ß-catenin signaling pathway plays a key role in the self-renewal of tissues during normal cell turnover. HPV deregulates this activity enhancing the epithelial-mesenchymal transition (EMT) of cancerous cells. The process of EMT allows cancer cells to suppress epithelial features and leads to increased cellular migration or cell renewal.[11] When the Wnt/ß-catenin pathway becomes active due to the presence of HPV, ß-catenin accumulates and accelerates the EMT process. This is a crucial pathway for the survival of HPV related cervical cancer cells.[2,16] By blocking the *Wnt/ß-catenin* pathway gefitinib can stop the EMT process and induce cell apoptosis and cell cycle arrest of cancerous cells.[16] The use of gefitinib for the

treatment of HPV related cervical cancer is in clinical trials. The results have shown gefitinib to be a promising therapeutic option for the future treatment of HPV related cancer.[11]

Discussion

Targeted molecular therapy has shown to be successful compared to traditional cancer therapies. Within the past ten years many molecular targeted therapies have been developed that successfully increase patient survival and decrease the rate of disease recurrence. One example is the drug imatinib. Imatinib is considered one of the more successful molecular targeted therapies developed for treating leukemia and gastrointestinal tumors without the negative side effects of chemotherapy.[12] Targeted therapy focuses on specific genetic alterations in various types of cancers making it more effective, highly specific, and more tolerable than other therapeutic methods such as radiotherapy or chemotherapy. Although chemotherapy is effective, it deals with rapidly dividing cells, destroys both cancerous and normal cells, and can result in long term toxic side effects for the patients making it a less desirable option.[6,15] Molecular targeted therapy is successful independently and in combination with traditional chemotherapy. Studies have shown that combining molecular targeted therapy with chemotherapy can decrease the development of therapeutic resistant cancer cells and successfully reduce tumors when compared with the treatment of cancer patients receiving a single drug therapy.[6] Molecular targeted therapy also reduces the likelihood of disease recurrence. By developing drugs to target the molecular pathways responsible for producing treatment resistant cancer cells, aggressive carcinoma cells can successfully be destroyed and increase a patient's overall survival rate.[7]

Although molecular targeted therapy is promising, it does have limitations. The high specificity of a molecular target limits the broad use of the drug in cancer treatment. Targeted therapy is effective when the drug targeted biomarker is responsible for progression of the patient's cancer.[6] Cancer can be unpredictable. There are numerous causes or genetic mutations that are responsible for the progression of cancer. A drug with one specific molecular target will not work on every cancer and as a result, will not be effective for the treatment of every patient. It is essential to understand the biology behind HPV related cancers when selecting the molecular targets that will be beneficial to the most patients.

Another limitation associated with targeted therapy is the development of drug resistance. Resistance has been identified upon initial cancer diagnosis due to the presence of drug-resistant mutations or a patient may develop a drug resistance during progression of the disease.[17] Mutations present in the PI3K pathway have been associated with the development of ceftuximab resistance during therapy. In HPV patients specifically, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PI3KCA*) mutations cause uncontrollable cell growth and deregulates the PI3K pathway. This specific mutation is associated with poor prognosis and treatment response when compared to patients without the mutation.[5] Clinical trials aimed at preventing cetuximab resistance are utilizing combination treatments with additional molecular targeted therapies such as mesenchymal epithelial transition (MET) and proto-oncogene tyrosine-protein kinase (SRC) inhibitors.[14] Cetuximab resistance has also been linked to the nuclear accumulation of EGFR which increases cellular proliferation through SRC signaling. This results in the patient becoming desensitized to cetuximab therapy. Clinical studies have found that nuclear translocation of EGFR can be prevented by using additional molecular targets such as an SRC family kinase (SFK), non-receptor tyrosine kinases responsible for signaling, to overcome resistance and increase cell death.[11,13]

A common mutation causing resistance towards gefitinib therapy is the Thr790Met (*T790M*) substitution. This mutation replaces a threonine (T) with a methionine (M) at the

entrance of the adenosine triphosphate (ATP) binding site preventing TKIs from binding.[18] Over half of all lung cancer patients treated with gefitinib will develop a *T790M* mutation at the beginning of disease progression.[17] Although this is common in lung cancer cases, that does not necessarily mean that *T790M* mutations will occur in HPV patients. However, since gefitinib is still in the clinical trial phase for HPV, further research will be required to determine if *T790M* will play a significant role in gefitinib resistance in the treatment of HPV patients.

Conclusion

The recent advancements in molecular targeted therapy for HPV related cancers is a promising therapy that can be prescribed individually and in combination with chemotherapy. Disease recurrence remains a cause of HPV related cancer death.[2] By implementing targeted molecular therapy, it is possible to decrease the likelihood of disease recurrence by targeting specific molecular pathways responsible for producing therapy resistant cancer cells.[7] Cetuximab and gefitinib have provided promising evidence for safe and effective treatment options for patients with HPV related cancer.

Cetuximab has proven to be a safe and effective FDA approved molecular targeted treatment option for HPV related HNSCC. It is responsible for an increase in the overall survival rate of patients with both recurrent and locally invasive cancers.[14] Cetuximab has provided additional therapy options to patients and has demonstrated the effective use of molecular targeted therapy in the treatment HPV related cancer.[13] Clinical trials testing gefitinib on cases of advanced HPV related cervical cancer have shown the drug to be safe and effective therapy. The high expression of EGFR in cervical cancer facilitates the binding of gefitinib leading to the destruction of cancerous cells.[11] There is great potential for the use of molecular targeted therapy in the treatment of HPV related cancer as well as other cancers. However, the development of drug resistance remains problematic and indicates a need for the development of additional targeted therapies to be used independently or in combination with existing treatments.

Various studies have shown that combining different drugs as part of a patient's therapy provides an improvement in treatment outcomes and decreases the development of drug resistance. Combining chemotherapy or additional molecular therapy targeted drugs provides a mechanism to potentially combat the development of drug resistance and improve a patient's survival rate.[6] With the limited options available for molecular therapy in HPV cancer, additional research is required to develop efficient targeted therapies.[5] Given that the genetic makeup of each patient's cancer can be different, the development of new molecular targeted therapies has the potential to eliminate invasive and toxic treatments while simultaneously paving the way for advancements in precision medicine.[6]

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