

Oncolytic virotherapy for anaplastic thyroid cancer: mechanisms, challenges, and future prospects

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Abstract. Anaplastic thyroid cancer (ATC) remains one of the most aggressive and treatment-resistant forms of thyroid cancer, with a near-zero 5-year survival rate. This review explores the potential of oncolytic virotherapy as a novel treatment approach for ATC. It discusses the mechanisms by which oncolytic viruses selectively target and lyse cancer cells, stimulating both innate and adaptive immune responses. The review highlights the challenges facing current virotherapy strategies, including biosafety concerns, limited bioavailability due to the blood-brain barrier, and potential adaptive immune resistance. To address these limitations, the author examines promising improvements in virus delivery and efficacy, such as focused ultrasound techniques, nanotechnology-based delivery systems, and combination therapies with immune checkpoint inhibitors and CAR-T cells. By integrating these advancements, oncolytic virotherapy shows potential to overcome the current treatment barriers in ATC, offering hope for improved patient outcomes. This review underscores the rapid progress in the field and emphasizes the need for continued research to optimize oncolytic virotherapy for ATC treatment.

Keywords: Anaplastic thyroid cancer, Oncolytic virus, Solid tumor.

1. Introduction

Thyroid cancer is the world's 10th most diagnosed cancer, accounting for 2.2% of the total predicted incidence in 2024 and 0.4% of cancer-related mortality. According to SEER data from 2024, thyroid cancer has a remarkably high relative survival rate of 98.4% between 2014 and 2020, making it seemingly less malignant compared to cancers like prostate or lung carcinoma [1]. Thyroid cancer is typically categorized into four main subtypes based on histology: papillary (PTC), medullary, follicular, and anaplastic (ATC), with each accounting for approximately 90%, 2%, 6%, and 1% of all thyroid cancer cases, respectively [2]. However, recent advances in understanding genetic drivers have led to a more nuanced classification, particularly recognizing anaplastic and poorly differentiated papillary thyroid cancers as de-differentiated forms, largely driven by mutations in BRAF and RAS.

Differentiated thyroid cancers generally have a high survival rate, with promising prognoses and favorable responses to established treatments like radioactive iodine (RAI) and surgery. Specifically, PTC and FTC exhibit 5-year survival rates of 99.1% and 92.7%, respectively. In stark contrast, poorly differentiated subtypes may reduce the 5-year survival rate to 50%, and ATC, the most severe subtype, is associated with nearly 0% 5-year survival [3]. The high mortality in de-differentiated thyroid cancers is primarily due to the loss of normal phenotypic features, leading to treatment resistance. As a result, while treatments for differentiated thyroid cancers are well-established, the failure of existing therapies

for de-differentiated subtypes highlights the urgent need for improving current treatments or developing novel approaches focused on these more aggressive forms of thyroid cancer.

This review aims to evaluate the limitations of existing treatment strategies for de-differentiated thyroid cancer and propose potential novel therapeutic approaches. By addressing these areas, the review seeks to contribute to the advancement of targeted therapies and improved outcomes for patients with aggressive forms of thyroid cancer.

2. Treatment

2.1. Conventional treatment failures

Radioactive iodine (RAI) was first introduced in the 1940s for the treatment of thyroid carcinoma. It uses the radioactive isotope iodine-131 (^{131}I), with a half-life of about 8 days [4]. When administered, RAI is transported into thyroid cells by the sodium-iodide symporter (NIS), integrating into the normal T3 and T4 synthesis pathways facilitated by thyroid peroxidase. This process ultimately induces cytotoxicity and apoptosis in the cancerous cells [5].

However, the effectiveness of RAI in treating differentiated thyroid carcinoma heavily depends on the normal expression and function of transport proteins like NIS. Resistance to RAI is likely to develop when these transport proteins are abnormally expressed or mislocalized. Additionally, RAI therapy is associated with several undesirable side effects. On one hand, RAI can inadvertently damage non-cancerous thyroid cells, leading to hypothyroidism instead of the desired euthyroidism. In some cases, it may also induce the transformation of viable thyroid cells into oncocytes or lead to other malignancies later in life [6]. On the other hand, clinical trials have linked RAI administration to adverse effects such as diarrhea, weight loss, endocrine dysfunction, and immunosuppression, which compromise the overall well-being of patients during treatment.

Given that the treatment for differentiated thyroid cancer is relatively well-established, the need for developing novel treatments for de-differentiated thyroid cancer becomes crucial. These novel therapies could potentially improve life expectancy and manage further malignancies. Therefore, this review will focus on discussing the emerging field of oncolytic viruses as a promising alternative.

2.2. Oncolytic Viruses

Oncolytic viruses represent a novel category of immunotherapy. These viruses possess surface proteins, tail sheaths, and genetic material enclosed in their cores, allowing them to selectively infect tumor cells. They can have single or double-stranded DNA or RNA genomes, which lead to cell lysis and an immunogenic cell death response. Oncolytic viruses offer two inherent advantages: their ability to bypass cellular defense mechanisms through the expression of complementary surface proteins and their potential for genetic modification to enhance functionality and selectivity [7].

2.2.1. Basic mechanism: targeting. The selectivity and functionality of oncolytic viruses can either occur naturally or through artificial modifications [7].

Natural selectivity is often due to the virus's affinity for abnormally upregulated surface molecules on cancer cells, which are employed by these cells as survival strategies (e.g., to evade apoptosis or immune detection). This affinity makes cancer cells more susceptible to oncolytic viruses, enabling viral entry and subsequent lysis. For instance, although CD46 is associated with immune evasion in malignant cells, measles virus utilizes this receptor for cell entry due to its natural affinity. Moreover, oncolytic virus therapy includes a diverse range of viral vectors targeting various oncogenic pathways and proteins, addressing issues like immune evasion, metastasis, and angiogenesis [7].

Oncolytic viruses also exploit the reduced anti-viral responses in cancer cells. Normal cells exhibit interferon responses and DNA/RNA degradation upon viral infection, which results in immunogenicity and viral clearance. However, aggressive cancer tumors often have dysfunctional interferon type I signaling pathways, which aids in immune evasion and reduces the inhibitory effects of interferons. Therefore, oncolytic viruses can selectively infect and replicate within these aggressive cancer cells,

sparing normal cells and offering a more targeted approach compared to conventional chemotherapy or immunotherapy. Additionally, the constitutive suppression of the MAP kinase pathway in thyroid cancer impairs PKR phosphorylation and protein synthesis inhibition, facilitating oncolytic viral replication, as seen with reovirus. Other oncolytic viruses may leverage increased tumor metabolism and protein production for enhanced targeting [8].

Engineered oncolytic viruses can further enhance specificity and functionality. By incorporating larger viral genomes, these viruses can be modified to include functions not present in native viruses. For example, adenoviruses can be engineered to express E1A, an Rb-mediated cell cycle arrest inhibitor, to promote viral replication and oncolysis specifically in tumor cells, while allowing normal cells to undergo Rb-induced apoptosis to prevent further infection. Other adenoviral subtypes can proliferate in tumor cells by coupling E1A expression to human telomerase reverse transcriptase or by facilitating E2F binding in the absence of Rb.[8]

Viruses can also be tailored to target elements of the tumor microenvironment (TME). The TME often exhibits the Warburg effect, characterized by abnormally low pH due to accelerated metabolism. This environment can produce oxidative species that interfere with radiotherapy and reduce the effectiveness of monoclonal antibodies. Engineering viruses to include hypoxia-sensitive promoters linked to E1B expression, or coupling E1A to human telomerase reverse transcriptase, can enhance viral replication within the TME [9].

Additionally, engineered viruses can target apoptosis mechanisms. Pro-apoptotic strategies can be used to treat metastatic tumors, such as using HSV-1 thymidine kinase (TK) controlled by a tumor-specific promoter to localize toxicity and increase therapeutic efficacy. Viruses can also delay cellular apoptosis to allow more extensive replication by altering key downstream regulators, like inactivating p53 or pRb. Conversely, in tumor cells, viral particles can induce lethal anti-tumor effects even in the absence of p53-related apoptosis pathways [9].

2.3. Basic mechanism: effect

Oncolytic viruses (OVs), whether genetically modified or naturally occurring, can directly lyse tumor cells due to defective antiviral pathways, such as interferons or PKRs. Following the lysis of infected tumor cells, these viruses can spread rapidly to neighboring uninfected cells, thereby amplifying their therapeutic effect [10].

The oncolytic effect is also enhanced by the secretion of tumor-derived exosomes, which may contain viral particles, proteins, or genetic materials that contribute to further lysis and infection. These exosomes may function similarly to OBP-301, inducing apoptosis and autophagy, which accelerates the viral replication cycle. Flow cytometry and western blotting analyses have demonstrated the independent efficacy and tropism of these exosomes [11].

Oncolytic viruses can interact with both innate and adaptive immunity. They may induce the release of pathogen-associated molecular patterns (PAMPs), such as viral capsids, genetic material, or proteins, stimulating immune responses or causing immunogenic cell death (e.g., apoptosis, necroptosis, or pyroptosis) by increasing endoplasmic reticulum stress and releasing damage-associated molecular patterns (DAMPs). This process creates a pro-inflammatory environment that can transform tumors. Immune cells, such as NK cells, are recruited to the tumor site and can lyse infected cells, further amplifying innate immunity. On the adaptive immunity front, tumor-specific T-cell responses are primed through the release of antigenic epitopes from oncolytic virus-mediated oncolysis, which leads to antigen presentation, antibody production, and activation of T-cells and B-cells to induce local or systemic tumor regression.

Finally, oncolytic viruses can target the extracellular matrix (ECM), which constitutes about 60% of solid tumor mass and forms a barrier around tumor cells that reduces viral bioavailability. Modifications to enhance oncolytic virus interaction with cancer-associated fibroblasts (CAFs) and increased sensitivity through elevated FGF2 production have shown potential. Additionally, oncolytic viruses can infect and lyse tumor vasculature and neo-vasculature, with genetically modified viruses displaying the capability to disrupt existing tumor vasculature and systems [12].

3. Limitations of existing anaplastic thyroid cancer treating virotherapy

Given the limited number of clinical trials on virotherapy for ATC, information about its limitations remains scarce. However, insights can be drawn from virotherapy studies in other solid tumors and brain tumors, as ATC shares similarities in pathophysiology with these conditions.

One potential limitation of virotherapy for ATC is biosafety. In cases where the immune system is compromised, there is a risk of uncontrollable proliferation of oncolytic viruses. This risk is particularly pronounced in patients who have undergone radiotherapy or related virotherapies, potentially leading to the presence of viral titers in organs such as the spleen or heart, as observed in studies using cisplatin and paclitaxel in mice. Since oncolytic viruses are often administered to patients with radioiodine-refractory disease, the immunosuppressive effects of RAI therapy could exacerbate issues, potentially resulting in neural toxicity or damage to normal thyroid cells, which could cause endocrine dysfunctions. Although preclinical studies have demonstrated the potential to mitigate such risks by removing harmful genes from viruses (e.g., deleting the vaccinia growth factor or E1 gene from adenoviruses), this often comes at the cost of reduced efficacy against cancer cells, creating a challenging trade-off [13].

Transportation and bioavailability of oncolytic viruses for ATC treatment also face significant challenges. The blood-brain barrier (BBB), known for its impermeability to large therapeutic molecules (rejecting 100% of them) and most small molecules (98%), presents a major hurdle. Endothelial cells in the BBB act as a barrier to diffusion due to the absence of transcellular pores, which limits the transportation of oncolytic viruses from blood vessels [14]. Additionally, the BBB's tight junctions and the regulation of vesicle formation and cellular polarity by pericytes further restrict the movement of polar molecules and macromolecules. Research has shown that solid tumors also face issues with poor perfusion due to a dense extracellular matrix (ECM) that regulates pore sizes and exerts abnormal interstitial fluid pressure, which hampers viral penetration. These barriers contribute to reduced bioavailability of oncolytic viruses, leading to diminished efficacy and potentially suboptimal therapeutic outcomes [15].

Another limitation is related to the adaptive immune response. The effectiveness of oncolytic viruses in priming adaptive immunity may be constrained by factors such as ineffective T-cell infiltration and antigen loss or escape. In ATC, the ability of oncolytic viruses to elicit a robust T-cell response can be compromised by the tumor's immunosuppressive microenvironment, which may lead to inadequate immune activation and reduced therapeutic efficacy [10].

4. Improvement

4.1. Focused ultrasound (FUS)

Many viruses struggle to penetrate the BBB, which complicates the delivery of therapeutic agents such as monoclonal antibodies (mAbs) to brain tumors. However, this challenge can be addressed by improving BBB permeability through various methods. Among these, FUS combined with intravenous microbubble (MB) administration offers a promising non-invasive solution. Compared to traditional methods, which are limited by poor spatial resolution, invasiveness, or complex biochemical designs, FUS provides a more precise and less invasive approach.

FUS works by utilizing cavitation and thermal energy to temporarily increase BBB permeability without causing extensive tissue damage. This effect is enhanced by using MBs, which reduce the acoustic power required by lowering the cavitation threshold of the vasculature, thus minimizing skull heating and enabling safer transcranial ultrasound administration. FUS can be precisely targeted with the aid of MRI technology, allowing visualization of regions such as implanted tumors through T1-weighted imaging with gadolinium contrast. Following FUS treatment, MBs carrying oncolytic viruses and modified T-cells are dispersed in the circulatory system. They travel to and penetrate the targeted area, increasing the concentration and bioavailability of therapeutic agents while reducing off-target effects and neurotoxicity. The MBs respond to the compression and rarefactions of the ultrasound waves, leading to dilation or constriction of vessel walls and thus enhancing permeability [16].

4.2. Nanotechnology

Nanotechnology offers innovative approaches for virus delivery, with several nanoparticle-based systems already on the market and others still under development. Nanoparticles, which include liposomes, micelles, polymer nanoparticles, and inorganic materials, typically range from 10 to 150 nm in size, providing significant advantages as drug carriers. The benefits of nanoparticle delivery are substantial:

- Protection of proteins from premature degradation or denaturation in the biological environment.

- Enhanced systemic circulation half-life of viruses with poor pharmacokinetic properties.

- Controlled and sustained release, maintaining therapeutic concentrations of oncolytic agents while minimizing the risk of infecting normal cells.

- Targeted delivery to diseased tissues, cells, and intracellular compartments, improving the safety and efficacy of biological therapeutics.

The success of nanoparticle formulations for small molecules such as doxorubicin (Doxil and Myocet), daunorubicin (DaunoXome), paclitaxel (Abraxane), and amphotericin B (Ambisome) demonstrates the potential of nanoparticle technologies for protein delivery and underscores their promise for enhancing virus-based therapies [17].

4.3. Combination therapy

Combination therapy represents a promising strategy for addressing complex diseases like ATC when novel oncolytic viruses are not yet available. This approach involves integrating various therapeutic modalities to activate multiple mechanisms that target cancer cells, disrupt the tumor microenvironment, and counteract resistance or metastasis. By combining therapies, it is possible to overwhelm the tumor's defense mechanisms and improve treatment efficacy.

One key advantage of combination therapy is its ability to alter the tumor's immunosuppressive environment, potentially converting the patient's immune system from a suppressed to an activated state that actively targets tumors. This method relies on existing drugs and therapies, reducing the time and costs associated with developing and testing new treatments. Clinical trials have consistently shown that combination therapies often yield better results than individual treatments.

For treating ATC with oncolytic viruses, combining these viruses with T-cells and CAR-T cells has shown promise. Engineered oncolytic viruses can aid the delivery and activation of CAR-T or TCR-T cells within tumors, enhancing the efficacy of adaptive immunity. To address chemokines secreted by tumors and stroma that diminish T-cell specificity, OV's can be genetically modified to express chemokines, activating memory cells and cytotoxic T lymphocytes. For instance, in studies by Moon et al., the use of VV.CXCL11 has demonstrated significant antitumor effects and improved T-cell migration in solid tumors. Additionally, oncolytic viruses can facilitate T-cell expansion by overcoming the hostile tumor microenvironment and carrying chemokines more efficiently. A few studies supported the efficacy of cytokine-carrying oncolytic viruses to aid CAR-T, such as genetically engineered oncolytic adenovirus can work with tumor-infiltrating lymphocytes by expressing TNF- α to reshape an immunosuppressive tumor microenvironment into an immunologically favorable one by improving T-cell recruitment, functioning, macrophage polarization and dendritic cell maturation. TGF β receptor can be a potential target, and reduction of metastatic possibility can be reduced once suppressed with antagonist. In other studies, the viruses showed abilities to delay T-lymphocyte apoptosis, improve natural killer cell efficacy by improving persistence, and cause tumor growth inhibition [10].

The use of oncolytic viruses may also improve the specificity and recognition by avoiding target loss. As previously mentioned, the tumor microenvironment can be highly immunosuppressive and dysfunctions CAR-T or TCR-T cell recognition mechanism by heterogeneous antigen overexpression or downregulation, while oncolytic viruses provide a solution by coupling with bispecific antigen engager to cope with existing targets. In the example of FR- α expression loss, bispecific antigen engagers can target multiple tumor targets, such as EGFR and FR- α simultaneously, making CAR-T treatment more successful; prospective tri-specific or multi-specific antigen engagers may function alike previously mentioned bispecific engager, shedding a light to immunotherapy combination.

Alternatively, certain subtypes of oncolytic virus may also deliver targets into or induce expression of targets within the solid tumor, causing improved cytotoxicity and formation of immunological memory [10].

Eventually, oncolytic viruses also showed potential to overcome exhaustion of CAR-T or TCR-T cells. Upregulation of inhibitory receptors like the PD-1 causes inactive phenotypes of T-cells and reduction of immune response, causing reduction to efficacy. OV's can act as vector for PD-1 competitive inhibitors, as it carries anti-PD-L1 blocking mini antibody which becomes expressed with high superiority following viral infection, enhancing function of CAR-T in xenograft models [10].

5. Conclusion

To conclude, anaplastic thyroid cancer is still a difficult subtype of thyroid carcinoma to be treated. The properties of anaplastic thyroid cancer as a solid tumor causes a series of challenges. It led to the resistance to radioactive iodine treatment, and the necessity of improving existing oncolytic virus technologies due to biosafety, bioavailability and deficiency of monotherapy. Recent research has made progress by updating transportation techniques with focused ultrasound and nanoparticles, editing virulent genes to balance efficacy and safety, and enabling a diversity of oncolytic virus arming for improved conjugation with modified tumor infiltrating lymphocytes. Generally, oncolytic viruses are a rapidly improving and edge-cutting field, that shed a ray of hope to conquering the most severe type of thyroid, or even endocrine cancers; and prospective successes would be extremely valuable, which may considerably alleviate the pain of anaplastic thyroid patients and prolong life expectancy. Despite improving of its own medical efficacy, oncolytic viruses may also combine with recently emerging technology such as bio-informatics, data science and artificial intelligence to step toward an era of precision medicine, which largely improves prognosis and decision making of application of therapeutics to avoid side-effects.

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