ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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STING Activators in Cancer Care

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H&O What are STING activators, and how do they play a role in cancer immunotherapy?

RS The stimulator of interferon genes (STING) pathway plays a crucial role in the immune response to cancer. This pathway serves a vital function in the innate immune defense and for initiating antitumor immune responses.[1] STING, functioning as a cytosolic sensor of DNA in cells, triggers a cascade of events that ultimately leads to the production of type 1 interferons in preclinical models, alongside other cytokines that activate an immune response.[2] This cyclic process starts with a protein called cGAS, which is a cyclic cGMP-AMP synthase, binding to cytosolic DNA. This interaction with STING in the endoplasmic reticulum leads to downstream effects involving TANK-binding kinase 1 (TBK1), a kinase that phosphorylates interferon regulatory factor 3 (IRF3), ultimately resulting in the production of genes like beta interferon.

A decade ago, in 2014, preclinical data from Dr Thomas Gajewski's lab at the University of Chicago provided intriguing insights.[3] The research highlighted the critical role of the STING pathway in the development of a spontaneous antitumor immune response in preclinical mouse models. Unlike other pathways such as toll-like receptors (TLRs) or myeloid differentiation primary response protein 88 (MyD88), STING knockout mice exhibited accelerated tumor growth and a lack of T-cell activation. This discovery led to the hypothesis that STING activation could offer therapeutic benefits, which started a whole avalanche of therapeutics that were developed to activate this pathway.

A subsequent preclinical paper showed that using cyclic dinucleotides, which are synthetic paired nucleotides that can activate the pathway, produced potent antitumor immune responses in preclinical models.[4] These responses included regression not only at the injected site but also of uninjected tumors transplanted to other locations on the mouse that were not directly treated. Those models showed that the effect was driven by an immune response rather than solely by a direct cancer-killing effect. When attempts were made to reimplant the same mice that had been "cured" of these tumors, the tumors did not grow, indicating memory in the immune response. This comprehensive understanding of the STING pathway led to all these therapies that are now in the clinic, some of which have now been published.

H&O Which patients are most likely to benefit from STING activation?

RS The initial intent of STING activation treatment was to address patients whose tumors did not respond to immune checkpoint blockade with anti–programmed death 1 (PD-1) therapies. Although anti–PD-1 therapies have revolutionized cancer treatment and are now approved for more than 20 cancer types, a substantial number of patients do not respond to these treatments. This is partly owing to a lack of the initial immune-priming event that occurs even before treatment. The hope was that by inducing the STING pathway, it could lead to the generation of an antitumor immune response and the priming of T cells against the cancer in patients who lack this spontaneous effect in their tumors at baseline.

These drugs were developed as intratumoral injections, in which tumors were directly injected with cyclic dinucleotides, and as small-molecule agents. The expectation was

that patients who did not respond to anti–PD-1 therapy would benefit from STING activation. The goal was to induce a response either as monotherapy or in combination with anti–PD-1 therapy.

The ideal patient for a STING agonist is one with limited disease, particularly at sites that can all be injected. This is often limited to cutaneous tumors like melanoma. Occasionally, other cancers with accessible tumors that can be injected deeper with interventional radiology may be considered. Pragmatically speaking, patients with cutaneous tumors are most likely to benefit and have the easiest accessibility for injection.

H&O What are the advantages of STING agonists?

RS The primary advantage is that STING agonists target a novel, innate immune pathway that had never before been targeted, and might prove effective even in tumors that lack the initial, spontaneous antitumor immune response. Another aspect, which can be seen as both an advantage and disadvantage, is the direct injection within the tumor. Although it may be considered a disadvantage, the upside is evident in cases of mixed responses to anti–PD-1 therapy, in which one could theoretically directly target those tumors that are not responding or causing symptoms, without the need for systemic administration.

H&O What novel STING agonists are currently being developed?

RS There are dozens of STING agonists currently in development. The most recent approaches are: (1) varying the delivery mechanism; (2) creating antibody-drug conjugates (ADCs); and (3) administering in combination with other therapies. Many of these strategies are based upon the insights from the modest results published with the standard first-generation cyclo-dinucleotides used for intratumoral injection.

Enhanced delivery mechanisms include incorporating STING agonists within a lipid nanoparticle, adding elements like manganese ions, and employing different methods to create microbubbles during the injection to encompass the tumor more broadly. A challenge with clinical trials in which intratumoral injections are performed is that it is difficult to inject a tumor and encompass the entire tumor with the drug vehicle and not have degradation or leakage into systemic circulation. These pragmatic challenges are dependent on the type and location of the tumor.

The most exciting approach involves the developing STING agonists being modified for conjugation to an antibody. This allows for systemic drug administration while localizing drug delivery to tumors. The ADC approach limits systemic toxicity and overcomes limitations posed by tumor injection. It extends drug delivery to tumors that are challenging to reach with injections, particularly if they are located behind blood vessels or in areas that are impossible to reach by injection in the clinic or with interventional radiology. The ADC approach has been successful in many other domains, making it a logical choice for STING agonists based on the limited data we have seen.

Lastly, combination strategies are being employed that involve systemically administered or intratumoral STING agonists combined with treatments such as radiation therapy or other innate immune pathway–signaling agents. This raises questions about potential combinations with other innate pathway agonists, such as TLRs, to enhance the specificity of the effect. These considerations may shed light on why clinical data have not shown better outcomes thus far.

H&O Could you describe the most important results with STING activators that have been presented or published?

RS The most mature data that have been published are from a study that we conducted here at the University of Chicago with the STING agonist MIW-815, also known as ADU-S100, as a single agent in 47 patients with advanced solid tumors or lymphoma who had prior therapy.[5] We observed tumor regression in most of the injected lesions, which initially suggested promise. However, when the systemic response was assessed through imaging, the objective response rate (ORR) was disappointingly low, at just 2.1%. There was insufficient noninjected tumor regression with STING agonist monotherapy. The study demonstrated that the drug was rapidly absorbed from the injection site into the systemic circulation and had a short half-life. This realization prompted next-generation approaches aimed at improving drug retention within the tumor and saturating the tumor using better formulation techniques.

We also published a second phase 1 trial with the same drug given in combination with spartalizumab, an anti–PD-1 therapy.[6] Similar to the first study, this trial included patients with various solid tumors who had prior therapy. Patients received weekly injections into the tumor and an intravenous (IV) dose of spartalizumab every 4 weeks. Although the response rate was slightly better than that with monotherapy, it remained modest, at 10.4%. Notably, some responses did occur in patients who had prior PD-1 therapy, suggesting a potential synergistic effect beyond PD-1 therapy alone. As with the monotherapy study, we observed regression in many

injected lesions. This represents the most mature data that have been published to date, with ongoing studies and abstracts featuring newer agents. We eagerly look forward to seeing more results in the future.

H&O Could you describe the most important ongoing studies with STING?

RS Ongoing studies with STING can be broadly categorized into the 3 groups mentioned earlier: ADCs with STING, combination therapies involving radiation or other innate immune activators, and newer delivery techniques. Numerous drugs within all of these categories are currently under investigation.

Additionally, there is a noteworthy ongoing study in leukemia, which presents a different scenario compared to solid tumor injections. In leukemia, the cancer is accessible in the liquid compartment (ie, the blood). This opens the possibility that systemically administered STING could potentially provide benefits without being limited by the challenges of solid tumor injections or ADC therapy. This aspect holds promise, and I look forward to seeing the results.

H&O What are the side effects associated with STING activation, and how are they managed?

RS In clinical trials, side effects associated with STING activation align with expectations and are indicative of stimulating an immune response. Local injection site reactions, including pain, erythema, and inflammation, are common. In most cases, these reactions are tolerable, but there are occasionally instances where they pose more of a challenge, leading to the drug having to be paused. Cytokine release syndrome (CRS) can occur, as is the case with most innate immune-activating agents. Although this is on target and expected, no high-grade or serious cases were observed in published studies. The CRS symptoms reported were low-grade and manageable with the administration of IV fluids and monitoring, without the need for admission to the intensive care unit or advanced interventions. However, it requires close monitoring in ongoing STING agonist studies, as CRS can become a serious complication if inadequately identified and treated. When combined with other agents, additional considerations arise, including the potential systemic side effects of coadministered agents like anti–PD-1 immunotherapy.

H&O Where are we going next with STING?

RS The future direction for STING appears to be leaning toward ADC therapy. Although there is promise in enhanced delivery mechanisms, I am particularly hopeful for ADC approaches because they offer targeted and more efficient delivery. ADCs could potentially overcome challenges associated with the heterogeneity of injection techniques, relying less on the subjective art of tumor injection. Administered directly by IV, ADCs have the potential to address all tumors, making this approach highly promising.

Additionally, exploring different combination approaches to tackle resistance mechanisms is crucial. Although challenges with noninjected tumors not responding have been discussed pragmatically, the biological reasons behind this phenomenon are actively being investigated in preclinical research. Understanding why a potent immune response in a tumor does not lead to regression in distant tumors with similar antigens is a key area of study. This ongoing research is likely to uncover additional mechanisms that can be targeted to address resistance.

In summary, the field of STING is moving toward a future marked by ADC therapy and innovative combinations based on robust preclinical data. Despite modest early results, the hope is that these approaches will lead to greater success in the future.

Disclosures

Dr Sweis has received consulting fees from Astellas, AstraZeneca, Aveo, BMS, EMD Serono, Editas, Exelixis, Gilead, Eisai, Janssen, Loxo, Lilly, Mirati, Pfizer, Silverback, and Seagen; has received research support (to institution) from Ascendis, ALX Oncology, Astellas, AstraZeneca, Bayer, BMS, CytomX, Eisai, Genentech/Roche, Gilead, Immunocore, Jounce, Loxo, Lilly, Merck, Moderna, Mirati, Novartis, Pfizer, Pionyr, Pyxis, Scholar Rock, QED Therapeutics; has equity in Abbvie; and has patents: Neoantigens in Cancer, PCT/US2020/031357.

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