ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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PROTAC Drugs in Cancer Care

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H&O What are PROTACs, and how do they target proteins in cancer treatment?

PF Proteolysis-targeting chimeras (PROTACs) are a new class of drugs that, in my opinion, will revolutionize drug development for various diseases. PROTACs are heterobifunctional small molecules consisting of 2 ligands joined by a linker. One ligand recruits and binds to a specific protein, whereas the other recruits and binds to the recruiting ligase, leading to the degradation of the protein. The simultaneous binding of the protein of interest in the ligase by the PROTAC induces ubiquitination and subsequent degradation of the protein. This mechanism opens the possibility of potentially degrading any protein in the body if a ligand that binds to that protein is found. This is significant because preclinical experiments have been conducted since the 1990s to determine the effects of switching pathways or removing certain proteins on cellular behavior, and whether this is beneficial in treating diseases. Once clinical programs establish safety and efficacy, PROTACs could be useful in selectively removing proteins from cells to treat patients with cancer.

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H&O What sets PROTACs apart from traditional small molecule inhibitors?

PF PROTACs are different from other inhibitors in that rather than binding to and inhibiting the activity of a protein of interest, PROTACs directly eliminate the targeted protein via the ubiquitin-proteasome system. This mechanism is advantageous because the iterative nature of the PROTAC function potentially allows for lower drug doses and less off-target activity. One problem with inhibitors is that they often bind not only to the intended target but also to other proteins; this appears to be much less likely to occur with PROTACs. Additionally, PROTACs can eliminate the protein of interest without binding to its active site, which may allow for the degradation of previously undruggable targets. Traditional inhibitors typically bind to an active pocket or a site involved in some past activity. However, all that PROTACs need is an anchoring point on the protein, after which the whole system binds to the protein and starts degrading it. This finding suggests we do not need to focus on the active binding sites of a protein. Instead, we can look for binding sites for the drug to attach to the protein and initiate the degradation through the ubiquitin-proteasome system.

H&O In what cancer types or mutations are PROTAC-based therapies currently being studied?

PF Currently, clinical-stage PROTACs are being studied in breast cancer and prostate cancer. In breast cancer,

vepdegestrant is one such example, whereas, in prostate cancer, bavdegalutamide and ARV-766 are under investigation. Vepdegestrant shows promising activity in patients with both *ESR1* wild-type and *ESR1*-mutated breast cancer. It specifically targets the estrogen receptor, an area of recent interest because of the emergence of other inhibitors and degraders of the estrogen receptor. Thus, PROTACs designed for this purpose can serve as selective estrogen receptor degraders. Whereas resistance mechanisms involving accumulating *ESR1* mutations might enhance the effectiveness of other selective estrogen receptor degraders, vepdegestrant appears to work independently from these *ESR1* mutations. Additionally, there are PROTACs in development targeting proteins like BCL6, KRAS, and MEK in non–small cell lung cancer, colorectal cancer, pancreatic cancer, and other solid tumors. There is a lot of activity going on in the PROTAC developmental field now that clinical trials for breast and prostate cancer have shown good efficacy and a favorable toxicity profile.

H&O Which of these agents do you feel is the furthest along in development?

PF As a breast cancer specialist, I can say that vepdegestrant, which was developed by Arvinas and now with Pfizer, is furthest into development. It is currently in phase 3 studies in metastatic breast cancer. One of these studies, the VERITAC-2 study, is comparing vepdegestrant vs fulvestrant in patients with advanced breast cancer who have previously received treatment with a CDK4/6 inhibitor and endocrine therapy. This combination is considered the standard for patients with advanced hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer. The VERITAC-3 study is investigating vepdegestrant plus palbociclib (Ibrance, Pfizer) vs letrozole with palbociclib in patients who have not received any prior treatment for their advanced disease. Vepdegestrant is also being studied in the early breast cancer setting in a neoadjuvant study. This trial involves patients who have not undergone any prior anticancer treatment. Given the efficacy of vepdegestrant, there is an effort to explore its use in the early stages of breast cancer.

H&O Could you describe some of the most important results with PROTACs that have been presented or published?

PF Two years ago at the San Antonio Breast Cancer Symposium (SABCS), we learned about the efficacy of vepdegestrant from the first in-human studies. In heavily pretreated patients with hormone receptor–positive, HER2-negative breast cancer, we have seen a clinical benefit rate of 41%. Notably, these patients had previously received CDK4/6 inhibitor treatment and other anticancer therapies. Updated results were presented at the most recent SABCS and ASCO meetings, revealing additional findings from another cohort within the same study. Again, it showed a manageable adverse event profile, with very favorable toxicity. It appeared effective in managing therapy, showing evidence of clinical activity among these highly pretreated patients with a median of 3 prior therapies in the metastatic setting. The overall clinical benefit rate was approximately 37% for all patients and 47% for patients with an *ERS1* mutation. Further insights were presented at SABCS by Dr Erika Hamilton, who discussed the use of vepdegestrant in combination with other agents to enhance the treatment of hormone receptor–positive breast cancer patients in overcoming endocrine resistance.

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

PF There is substantial ongoing activity with PROTACs, particularly outside phase 3 trials. A noteworthy study is the I-SPY study, a well-known adaptive phase 2 trial in high-risk early breast cancer. It has arms for neoadjuvant vepdegestrant monotherapy and vepdegestrant with letrozole. Several combination studies have also been initiated based on encouraging preclinical data. For example, the TACTIVE-U open-label, phase 1b/2 umbrella study of vepdegestrant combined with abemaciclib (Verzenio, Lilly) in patients with advanced or metastatic breast cancer. The phase 1b part will evaluate the safety and tolerability to determine the recommended combination dose, and the phase 2 part will evaluate anticancer activity. Enrollment in this arm is ongoing. Similarly, the ribociclib (Kisqali, Novartis) part of the study is a phase 1b/2 trial investigating vepdegestrant with ribociclib, another CDK4/6 inhibitor, in patients with advanced hormone receptor–positive, HER2-negative breast cancer. The phase 1b part will evaluate the safety and tolerability to select a combination dose, and the phase 2 part will evaluate anticancer activity. That arm is also currently enrolling patients. Another example is a phase 1b/2 study of the CDK7 inhibitor samuraciclib in combination with vepdegestrant in patients with hormone receptor–positive, HER2-negative breast cancer. The phase 1b part will evaluate the safety and tolerability of samuraciclib plus vepdegestrant, and the phase 2 part will evaluate anticancer activity. Enrollment should begin later this year. Additionally, substances known to overcome antibody resistance, like everolimus, are also being tested. The TACTIVE-E study is a phase 1b study of vepdegestrant and everolimus in previously treated patients. Enrollment is ongoing.

H&O Are there any limitations to PROTACs, and how are researchers like yourself working to address them?

PF In situations where clinical data remain limited, researchers often turn to in vitro models. Mechanisms of acquired resistance to vepdegestrant have been assessed in vitro, which has led to the development of vepdegestrant-resistant breast cancer cell lines. These experiments using vepdegestrant-resistant breast cell lines have highlighted certain associated resistance factors. For example, the downregulation of the ER protein is pivotal because PROTACs degrade this protein. We have also shown an upregulation in HER2 family cycling, a known resistance mechanism to antiendocrine treatment. There was also observed potential for upregulated mitogen-activated protein kinase (MAPK) upsignaling, a pattern similar to other studies involving endocrine active substances. These in vitro models provide an initial insight into potential resistance mechanisms and indicate the populations in which these drugs might demonstrate efficacy. However, as the clinical data are still evolving, there is not much concrete evidence to build on at present.

Disclosures

Dr Fasching is a board member of TRIO (Translational Research in Oncology), which conducts clinical trials in cooperation with Arvinas.

Suggested Readings

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